(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 478 363 A2**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : **91308850.6**

(22) Date of filing : **27.09.91**

(51) Int. Cl.[5] : **C07D 211/22,** C07D 409/12, C07C 311/13, C07C 311/19, A61K 31/445

(30) Priority : **27.09.90 US 589130**
30.08.91 US 750647

(43) Date of publication of application :
01.04.92 Bulletin 92/14

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) **Novel sulfonamide fibrinogen receptor antagonists.**

(57) A series of non-peptide derivatives that are antagonists of the fibrinogen IIb/IIIa receptor and thus are platelet anti-aggregation compounds useful in the prevention and treatment of diseases caused by thrombus formation.

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BACKGROUND OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds being generally pharmacologically useful as anti-platelet aggregation agents in various vascular pathologies. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the sulfonamide compounds of the present invention act by blocking the molecular receptor site of the protein fibrinogen. Fibrinogen is a glycoprotein that circulates in the blood plasma, and whose platelet receptor site is glycoprotein IIb/IIIa. By blocking the action of fibrinogen at the receptor (glycoprotein IIb/IIIa), the compounds of the present invention interfere with platelet aggregation, which is a cause of many vascular pathologies. At the present time, there is a need in the area of vascular therapeutics for such a fibrinogen receptor blocking agent. By interfering with hemostasis, such therapy would decrease the morbidity and mortality of thrombotic disease.

Hemostasis is the spontaneous process of stopping bleeding from damaged blood vessels. Precapillary vessels contract immediately when cut. Within seconds, thrombocytes, or blood platelets, are bound to the exposed matrix of the injured vessel by a process called platelet adhesion. Platelets also stick to each other in a phenomenon known as platelet aggregation to form a platelet plug. This platelet plug can stop bleeding quickly, but it must be reinforced by the protein fibrin for long-term effectiveness, until the blood vessel tear can be permanently repaired by growth of fibroblasts, which are specialized tissue repair cells.

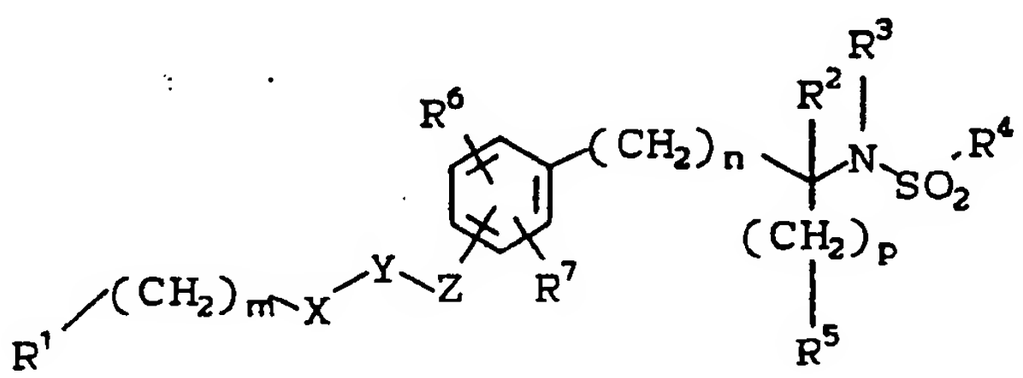
An intravascular thrombus (clot) results from a pathological disturbance of hemostasis. The thrombus can grow to sufficient size to block off arterial blood vessels. Thrombi can also form in areas of stasis or slow blood flow in veins. Venous thrombi can easily detach portions of themselves called emboli that travel through the circulatory system and can result in blockade of other vessels, such as pulmonary arteries. Thus, arterial thrombi cause serious disease by local blockade, whereas venous thrombi do so primarily by distant blockade, or embolization. These diseases include venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis and myocardial infarction, stroke, cerebral embolism, kidney embolisms and pulmonary embolisms.

There is a need in the area of cardiovascular and cerebrovascular therapeutics for an agent which can be used in the prevention and treatment of thrombi, with minimal side effects, including unwanted prolongation of bleeding in other parts of the circulation while preventing or treating target thrombi. The compounds of the present invention meet this need in the art by providing therapeutic agents for the prevention and treatment of thrombi.

The compounds of the present invention show efficacy as antithrombotic agents by virtue of their ability to block fibrinogen from acting at its platelet receptor site and thus prevent platelet aggregation.

SUMMARY OF THE INVENTION

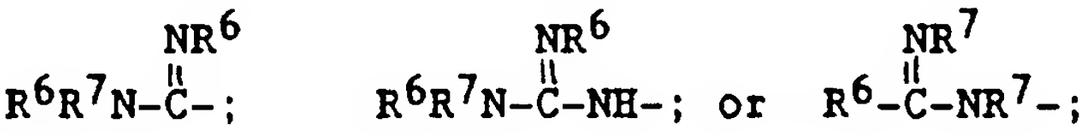
The present invention relates to novel compounds having the general structural formula I :

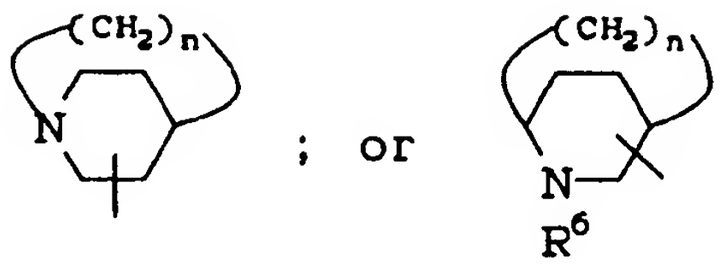


and the pharmaceutically aceptable salts thereof, wherein

R^1 is,

a four to eight member heterocyclic ring containing 1, 2 ,3 or 4 heteroatoms wherein said hetero atoms are N, O or S and wherein said hetero ring is optionally substituted at any atom by H, R^6 or R^7; NR^6R^7





wherein R^8 and R^7 are independently hydrogen and unsubstituted or substituted C_{0-10} alkyl and cycloalkyl wherein said substituents are

C_{1-10} alkoxy,
C_{1-10} alkoxyalkyl,
C_{1-10} alkoxyalkyloxy,
C_{1-10} alkoxycarbonyl,
C_{1-10} alkylcarbonyl,
C_{4-10} aralkylcarbonyl,
C_{1-10} alkylthiocarbonyl,
C_{1-10} aralkylthiocarbonyl,
thiocarbonyl,
C_{1-10} alkoxythiocarbonyl,
aryl,
a 5 to 6 membered saturated heterocyclic ring containing 1,2,3 or 4 hetero atoms wherein said heteroatoms are taken from the group consisting of N, O and S,
C_{1-4} alkanoylamino,
C_{1-6} alkoxycarbonyl-C_{0-6} alkylamino,
C_{1-10} alkylsulfonylamino,
C_{4-10} aralkylsulfonylamino,
C_{4-10} aralkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthio,
C_{4-10} aralkylthio,
C_{1-10} alkylsulfinyl,
C_{4-10} aralkylsulfinyl,
C_{1-10} alkylsulfonyl,
C_{4-10} aralkylsulfonyl,
aminosulfonyl,
C_{1-10} alkylaminosulfonyl,
C_{4-10} aralkylsulfonylamino,
oxo,
thio,
unsubstituted and mono- and di-substituted 1-ethenyl, 2-ethenyl and 3-propenyl wherein said substituents are selected from the group consisting of hydrogen, C_{1-10} alkyl and C_{4-10} aralkyl,
carboxy,
hydroxy,
amino,
C_{1-6} alkylamino,
C_{1-6} dialkylamino,
halogen, where halogen is defined as F, Cl, Br or I,
nitro, and
cyano,

and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said substituent is as previously defined for R^6 and R^7;

R^2 and R^3 are independently
hydrogen,
aryl and
unsubstituted and substituted C_{0-10} alkyl and cycloalkyl wherein said substituent is C_{1-10} alkoxyalkyl, aryl,

a 4 to 8 membered saturated heterocyclic ring system containing 1, 2, 3 or 4 heteroatoms, wherein said heteroatoms are taken from the group consisting of N, O and S,

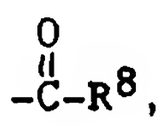
C_{4-10} aralkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthio,
C_{4-10} aralkylthio,
C_{1-10} alkylsulfinyl,
C_{4-10} aralkylsulfinyl,
C_{1-10} alkylsulfonyl,
C_{4-10} aralkylsulfonyl,
carboxy,
C_{1-10} alkylcarbonyl,
C_{1-10} alkylthiocarbonyl,
C_{4-10} aralkylcarbonyl,
C_{4-10} aralkylthiocarbonyl,
C_{1-6} alkoxycarbonyl,
C_{4-10} aralkoxycarbonyl,
C_{1-6} alkoxy,
C_{1-6} alkoxycarbonyl-C_{1-4} alkyl,
C_{4-10} aralkoxycarbonyl-C_{1-4} alkyl,
C_{4-10} aralkoxy,
C_{1-6} alkylamino,
C_{1-12} dialkylamino,
C_{1-6} alkanoylamino,
C_{4-10} aralkanoylamino,
C_{4-10} aralkylamino,

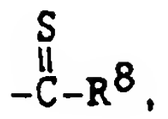
R^4 is

aryl,
C_{1-10} alkyl or cycloalkyl,
C_{4-10} aralkyl,
C_{1-10} alkoxyalkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthioalkyl,
C_{1-10} alkoxythioalkyl,
C_{1-10} alkylamino,
C_{4-10} aralkylamino,
C_{1-10} alkanoylamino,
C_{4-10} aralkanoylamino
C_{1-10} alkanoyl,
C_{4-10} aralkanoyl, and
unsubstituted or substituted C_{1-10} carboxyalkyl wherein said substituent is aryl or C_{1-10} aralkyl; further wherein any of the substituents for R^4 may be substituted by substituents selected from the group as defined for R^6;

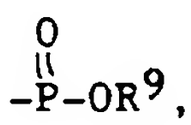
R^5 is

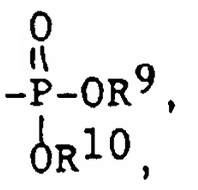
a four to eight member saturated or unsaturated heterocyclic ring containing 1, 2, 3 or 4 heterocyclic atoms wherein said heteroatoms are N, O and S and



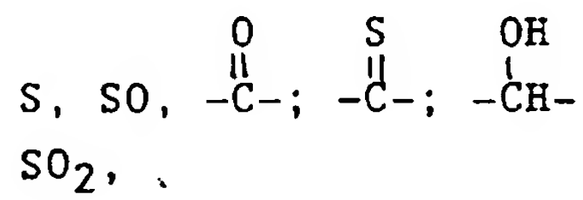


wherein R^8 is
hydroxy,
C_{1-10} alkyloxy,
C_{1-10} alkaryloxy,
C_{4-10} aralkyloxy,
C_{4-10} aralkylcarbonyloxy,
C_{1-10} alkoxyalkyloxy,
C_{1-10} alkoxyalkylcarbonyloxy,
C_{1-10} alkoxycarbonylalkyl,
C_{1-10} alkylcarbonyloxyalkyloxy,
an L- or D-amino acid joined by an amide linkage or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is esterified by C_{1-6} alkyl or C_{4-10} aralkyl,

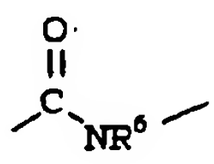


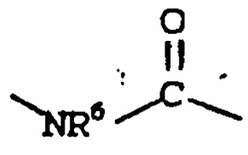


wherein R^9 and R^{10} are selected from the group consisting of hydrogen, C_{1-10} alkyl and C_{4-10} aralkyl;
X and Y optional substituents that, when present are independently
NR^6,
O,



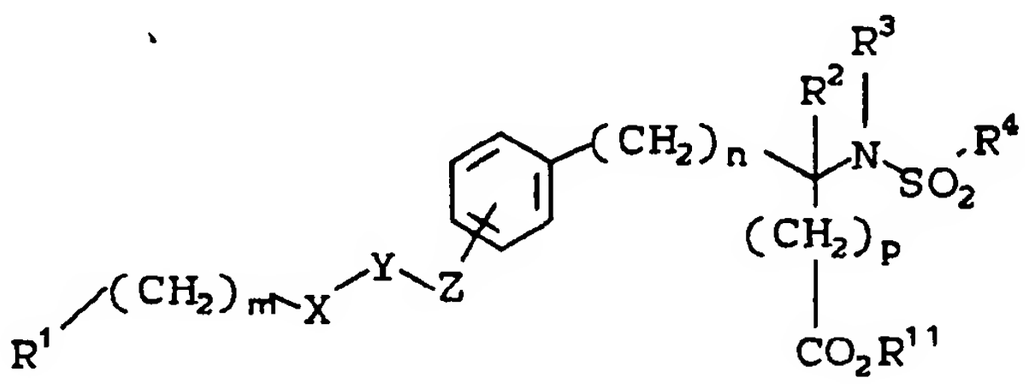
SO_2,
R^6R^7
-C=C-,
-C≡C-,
a 4- to 8-membered ring containing 0,1,2,3, or 4 heteroatoms chosen from N, O and S, wherein said ring is independently substituted at any atom with R^6,
aryl,





or
Z is an optional substituent that, when present, is independently chosen as defined for X and Y;
m is an integer of from zero to ten;
n is an integer of from zero to ten; and
p is an integer of from zero to three.

A preferred group of compounds of the present invention are those defined for general structural formula II as:



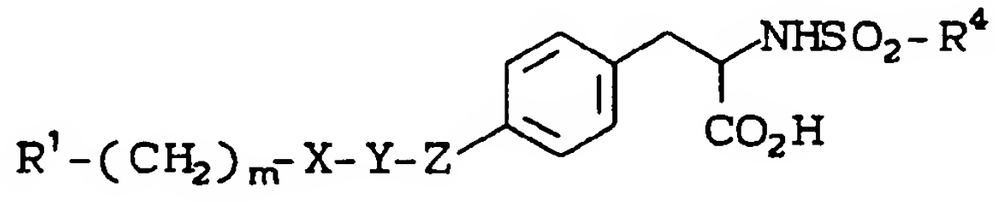
wherein
R^1 is
a five to six member heterocyclic ring wherein said heteroatoms are N, O or S and wherein said heterocyclic ring is optionally substituted by C_{1-5} alkyl; or
NR^6R^7 wherein R^6 and R^7 are independently hydrogen,
unsubstituted or substituted C_{1-10} alkyl wherein said substituent is
C_{1-10} alkoxycarbonyl,
aryl,
C_{0-5} dialkylamino-C_{1-10} alkyl,
C_{4-10} aralkyl,
and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said substituent is as previously defined for R^6 and R^7;
R^2 and R^3 are
hydrogen and
C_{1-4} alkyl, C_{4-10} aralkyl;
R^4 is
aryl,
C_{1-10} alkyl or cycloalkyl,
C_{4-10} aralkyl,
C_{1-10} alkoxyalkyl,
C_{1-10} alkaryl,
unsubstituted or substituted C_{1-10} carboxyalkyl wherein said substituent is aryl, C_{1-6} alkyl, or C_{4-10} aralkyl;
R^{11} is
hydrogen or
C_{1-10} alkyl;
X and Y are independently
aryl,
O,SO_2,

$$-CH=CH-;\ -\overset{O}{\overset{\|}{C}}NR^6-;\ -NR^6\overset{O}{\overset{\|}{C}}-;\ SO_2NR^6-;\ \text{or}\ -NR^6SO_2$$

a 5 or 6-membered ring containing 0,1 or 2 heteroatoms chosen from N or O;
Z is an optional substituent that, when present, is
O, SO_2, $-NR^6CO-$, $-CONR^6-$,
C_{1-10} straight or branched alkyl;

m is an integer of from zero to eight;
n is an integer of from zero to two; and
p is an integer of from zero to two.

A more preferred group of compounds of the present invention are those defined for general structure formula III as



wherein

R^1 is

a five or six membered heterocyclic ring wherein said heteroatoms are N and O and wherein said heterocyclic ring is optionally substituted by C_{1-5} alkyl;

NR^6R^7 wherein R^6 and R^7 are independently

C_{1-10} alkyl, or

C_{4-10} aralkyl

and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said stubstituent is as previously defined for R^6 and R^7;

R^4 is

aryl,

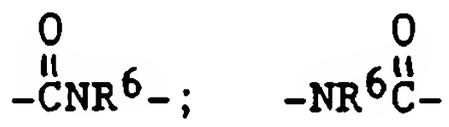
C_{1-10} alkyl or cycloalkyl, or

C_{4-10} aralkyl;

X and Y are independently

phenyl

O, SO_2



or a 5- or 6- membered ring containing 0 or 1 heteroatoms chosen from N or O;
Z is an optional substitutent that, when present, is

O, SO_2, $-NR^6CO-$, $-CONR^6-$, or $-CH_2-$; and
m is an integer of from zero to six.

DETAILED DESCRIPTION OF THE INVENTION

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

Acetate
Benzenesulfonate
Benzoate
Bicarbonate
Bisulfate
Bitartrate
Borate
Bromide
Calcium Edetate
Camsylate
Carbonate
Chloride
Clavulanate

Citrate
Dihydrochloride
Edetate
Edisylate
Estolate
Esylate
Fumarate
Gluceptate
Gluconate
Glutamate
Glycollylarsanilate
Hexylresorcinate
Hydrabamine
Hydrobromide
Hydrochloride
Hydroxynaphthoate
Iodide
Isothionate
Lactate
Lactobionate
Laurate
Malate
Maleate
Mandelate
Mesylate
Methylbromide
Methylnitrate
Methylsulfate
Mucate
Napsylate
Nitrate
Oleate
Oxalate
Pamaote
Palmitate
Pantothenate
Phosphate/diphosphate
Polygalacturonate
Salicylate
Stearate
Subacetate
Succinate
Tannate
Tartrate
Teoclate
Tosylate
Triethiodide
Valerate

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical reponse of a tissue, system or animal that is being sought by a researcher or clinician. The term "anti-coagulant agent" shall include aspirin, heparin and warfarin. The term "fibrinolytic agent" shall include streptokinase and tissue plasminogen activator.

The term "aryl" shall mean a mono- or polycylic ring system composed of 5- and 6- membered aromatic rings containing 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, and S and either unsubstitutued or substituted with R^6.

The term "alkyl" shall mean straight or branched chain alkane, alkene or alkyne.

The term "alkoxy" shall be taken to include an alkyl portion where alkyl is as defined above.

The terms "aralkyl" and "alkaryl" shall be taken to include an alkyl portion where alkyl is as defined above

and to include an aryl portion where aryl is as defined above.

The term "halogen" shall include fluorine, chlorine, iodine and bromine.

The term "oxo" shall mean the radical =O.

The term "thio" shall mean the radical =S.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardivascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. They may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardivascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GPIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko et. al., Amer. J. Physiol., 1987, 252:H, pp 615-621). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other application of these compounds include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures. They may also be used to prevent mycocardial infarction.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules, pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous, intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 1.0-100 mg/kg/day and most preferably 1.0 to 50 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesuim stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be for-

med from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The compounds of the present invention can also be co-administered with suitable anti-coagulant agents or thrombolytic agents to achieve synergistic effects in the treatment of various vascular pathologies.

The compounds of formula I can be prepared readily according to the following reaction Schemes and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative precedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

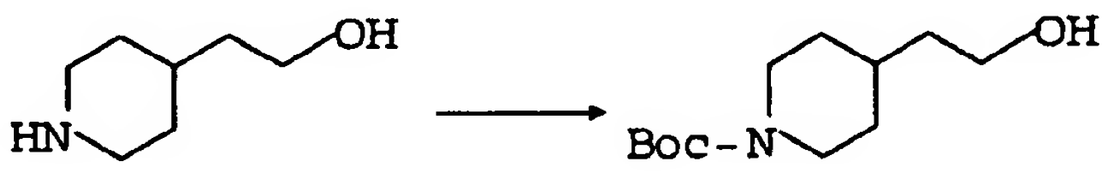
Reagent symbols have the following meanings:

BOC: t-butyloxycarbonyl
Pd-C: Palladium on activated carbon catalyst
DMF: Dimethylformamide
DMSO: Dimethylsulfoxide
CBZ: Carbobenzyloxy
CH_2Cl_2: Methylene chloride
$CHCl_3$: Chloroform
EtOH: Ethanol
MeOH: Methanol
EtOAc: Ethyl acetate
HOAc: Acetic acid
THF: Tetrahydrofuran

The source for the following compounds is as shown:

1. 

is described below.



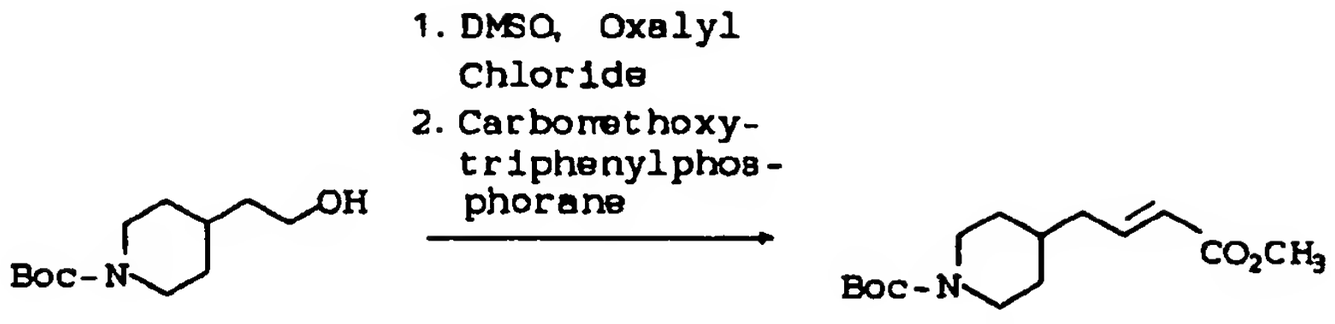
2-(4-N-t-Butyloxycarbonylpiperidinyl)ethanol

4-Piperidine-2-ethanol (Available from Aldrich) (130 g, 1.0 mole) was dissolved in 700 mL dioxane, cooled to 0° C and treated with 3 N NaOH (336 mL, 1.0 mole), and di-t-butylcarbonate (221.8 g, 1.0 mole). The ice bath was removed and the reaction stirred overnight. The reaction was concentrated, diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give 225.8 g of product (98%).

R_f = 0.37 in 1:1 EtOAc/Hexanes, ninhydrin stain

^1H NMR (300MHz, $CDCl_3$) δ 4.07 (bs, 2H), 3.7 (bs, 2H), 2.7 (t, J = 12.5 Hz, 2H), 1.8-1.6 (m, 6H), 1.51 (s, 9H),

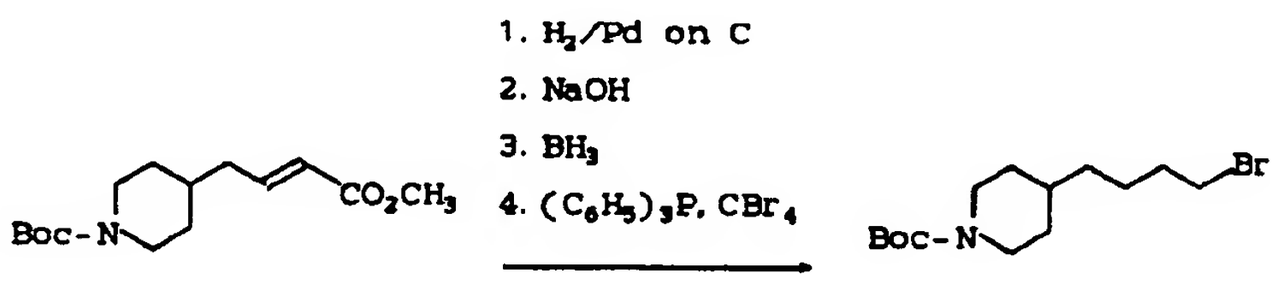
1.1 (ddd, J = 4.3, 12.5, 12 Hz, 2H).



Methyl 4-(4-N-t-butyloxycarbonylpiperidinyl)-but-2-enoate

Oxalyl chloride (55.8 mL, 0.64 mole) was dissolved in 1 L CH_2Cl_2 and cooled to -78° C under N_2. DMSO (54.2 mL, 0.76 mole) was added dropwise. After gas evolution had ceased, 2-(4-N-t-butyloxycarbonylpiperidinyl)ethanol (102.5 g, 0.45 mole) dissolved in 200 mL CH_2Cl_2 was added over 20 minutes. After stirring an additional 20 minutes, triethylamine (213 mL, 1.53 mole) was added dropwise and the cold bath removed. After 1 and 1/2 hours TLC showed starting material gone. Carbomethoxytriphenylphosphorane (179 g, 0.536 mole) was added and the reaction stirred overnight. The solution was diluted with 300 mL Et_2O, extracted once with 800 mL H_2O, twice with 300 mL 10% $KHSO_4$ solution, then once with 300 mL brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. Column chromatography (SiO_2, 5% EtOAc/Hexanes) yielded 78.4 g (62%) of pure methyl 4-(4-N-t-butyloxycarbonylpiperidinyl) but-2-enoate.

^{1}H NMR (300MHz, $CDCl_3$) δ 6.9 (ddd J = 15.6, 7,6, 7.6 Hz, 1H), 5.8 (d, J = 15.6 Hz, 1H), 4.0 (bs, 2H), 3.7 (s, 3H), 2.6 (t, J = 12.6 Hz, 2H), 2.1 (t, J = 7.4 Hz, 2H), 1.7-1.4 (m, 3H), 1.4 (s, 9H), 1.1 (m, 2H).



4-(4-N-t-Butyloxycarbonylpiperidinyl)butyl bromide

Methyl 4-(4-N-t-butyloxycarbonylpiperidinyl)but-2-enoate (36.2 g, 0.128 mole), was dissolved in 500 mL EtOAc. 10% Palladium on carbon (10 g) was added as a slurry in EtOAc and the reaction was placed under H_2 (in a balloon) overnight. The reaction was filtered through Solka-Floc, the cake washed with EtOAc and the ethyl acetate evaporated to give 34.7 g (90%) of methyl 4-(4-N-t-butyloxycarbonylpiperidin-4-yl)butanoate. TLC R_f = 0.69 in 30% EtOAc/Hexanes.

^{1}H NMR (300MHz, $CDCl_3$) δ 4.0 (bs, 2H), 3.6 (s, 3H), 2.60 (t, J = 12.3 Hz, 2H), 2.20 (t, J = 7.4, 2H), 1.6 (m, 4H), 1.40 (s, 9H), 1.40 (m, 1H), 1.20 (m, 2H), 1.0 (m, 2H).

The butanoate ester (45.3 g, 0.159 mole) was dissolved in CH_3OH and treated with 1 N NaOH (500 mL, 0.5 mole) overnight. The solvent was removed in vacuo, water was added and the solution washed with ether, then acidified with 10% $KHSO_4$ solution. The aqueous layer was washed with ether, the ether layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to give the corresponding acid as a clear oil (41.85 g, 97% yield).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.0 (bs, 2H), 2.6 (m, 2H), 2.25 (m, 2H), 1.6 (bs, 4H, 1.4 (s, 9H), 1.3-0.9 (9H).

This acid (20.4 g, 0.077 mole) was treated with borane (BH_3/THF, 235 mL, 235 mmole) in THF at 0° for 1 hour. NaOH (1N, 250 mL) was added dropwise and the solution stirred overnight. The resulting reaction mixture was concentrated to remove THF and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, filtered and evaporated to give the corresponding alcohol as 19.7 g of a colorless oil.

R_f = 0.7 in 2:1 ethyl acetate/hexanes.

^{1}H NMR (300MHz, $CDCl_3$) δ 4.1 (bs, 2H), 3.6 (t, 2H), 2.65 (t, 2H), 2.1 (bs, 1H), 1.65 (bs, 2H), 1.55 (m, 2H), 1.4 (s, 9H), 1.35 (m, 3H), 1.25 (m, 2H), 1.1 (m, 2H).

This alcohol (19.7 g, 76.5 mmole) was dissolved in THF and treated with triphenylphosphine (23.1 g, 88 mmole) and cooled to 0° C. Carbon tetrabromide (29.8 g, 89.9 mmol) was added in one portion, the cold bath was removed and the reaction stirred overnight. Additional triphenyl phosphine (11.71 g) and carbon tetrabromide (14.9 g) was added to drive the reaction to completion. The mixture was filtered and the liquid was diluted with ether and filtered again. After solvent removal the resulting liquid was adsorbed onto SiO_2 and

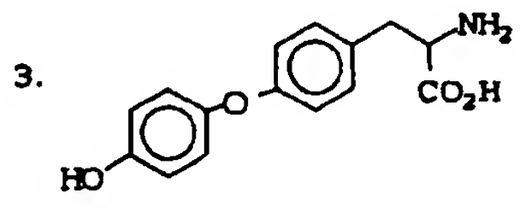
chromatographed with 5% EtOAc/Hexanes to yield 4-(4-N-t-butyloxycarbonylpiperidin-4-yl)butyl bromide as a clear colorless oil (20.7 g, 85% yield).

R_f = 0.6 in 1:4 ethyl acetate/hexanes

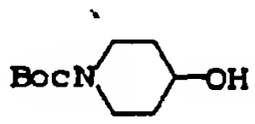
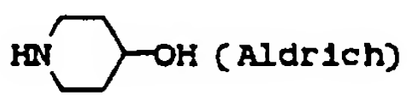
^{1}H NMR (300MHz, $CDCl_3$) δ 4.1 (bs, 2H), 3.4 (t, 2H), 2.65 (t, 2H), 1.85 (m, 2H), 1.65 (bd, 2H), 1.4 (s, 9H), 1.35 (m, 2H), 1.3 (m, 3H), 1.1 (m, 2H).

2.$BocNH(CH_2)_6Br$

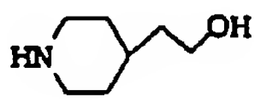
Commercial $H_2N(CH_2)_5CH_2OH$ was protected as the N-Boc derivative in standard fashion and this was converted to the bromide with Ph_3P/CBr_4 in THF. Utilization of starting amino alcohols of varying chain lengths provides the analogous halides in this manner.

3. 

Purchased from Sigma.

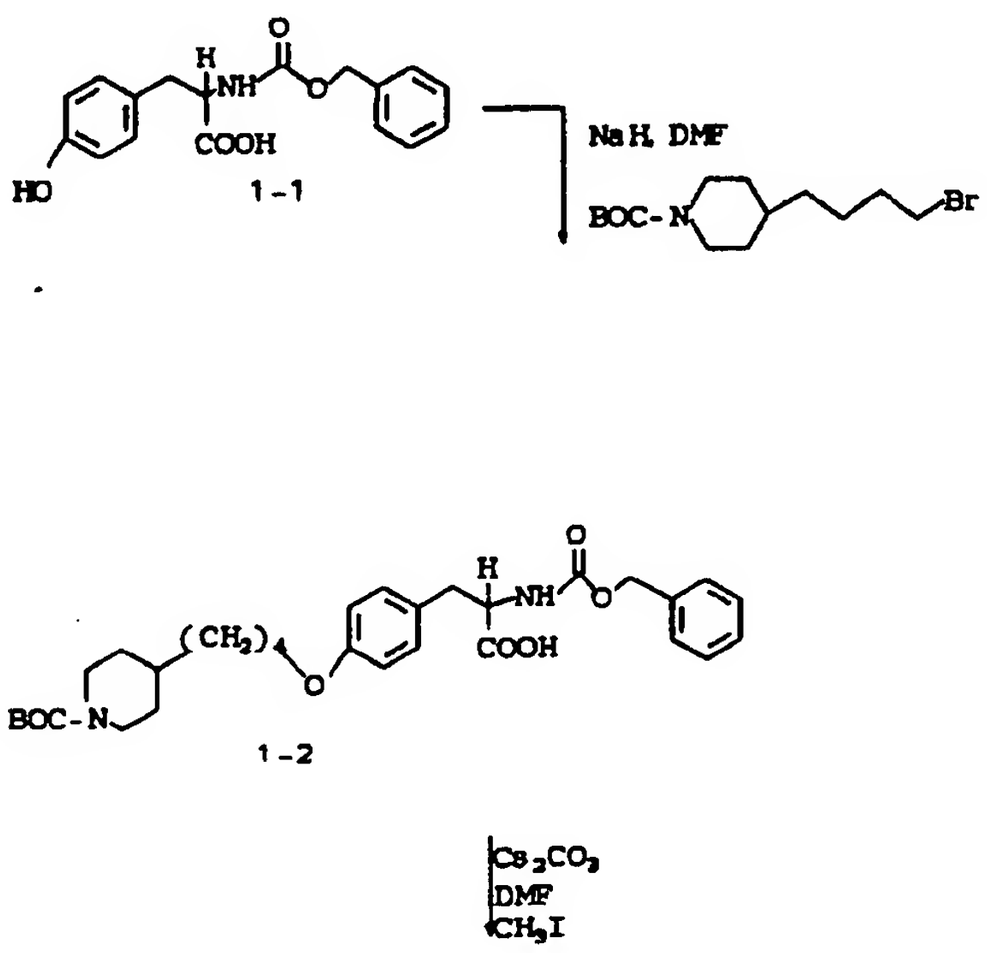
4.  

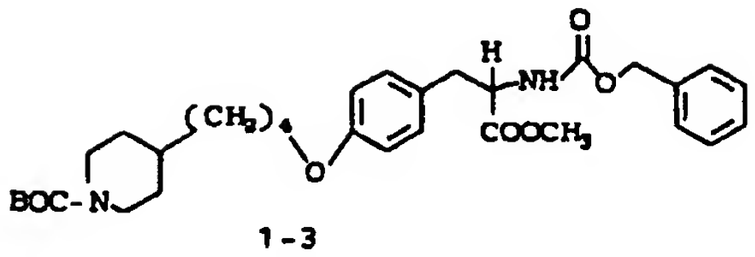
was N-Boc protected in the standard manner.

5.  

was N-Cbz protected in the standard fashion and converted to final product as described in US Serial No. 589,145.

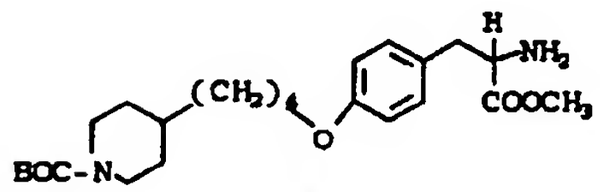
SCHEME 1



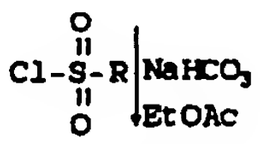


1-3

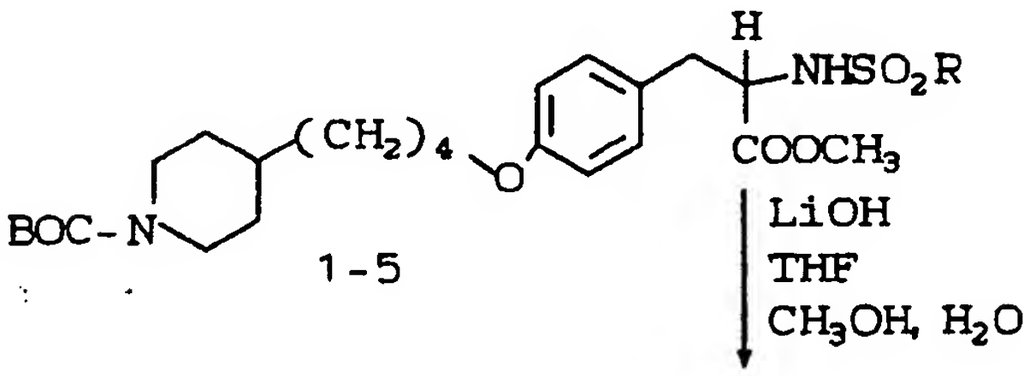
H_2, Pd/C
EtOH



1-4



1-5



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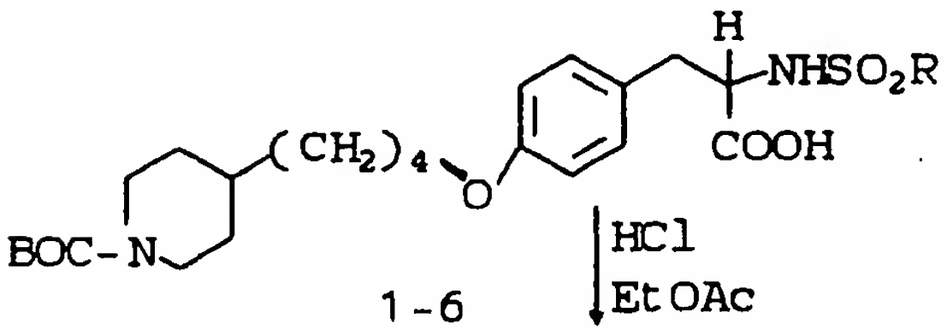
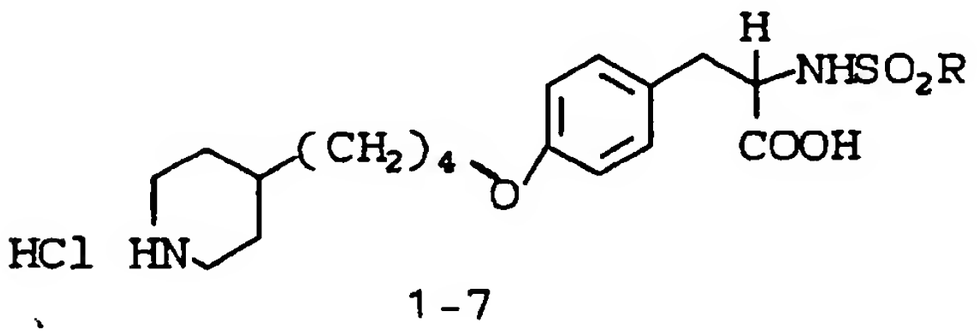
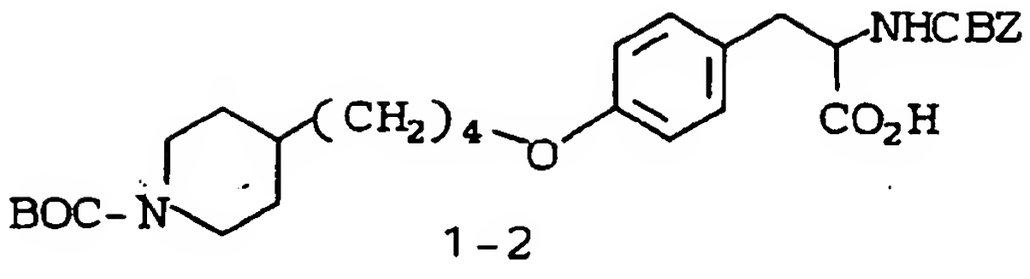


1-6



1-7

EXAMPLE 1



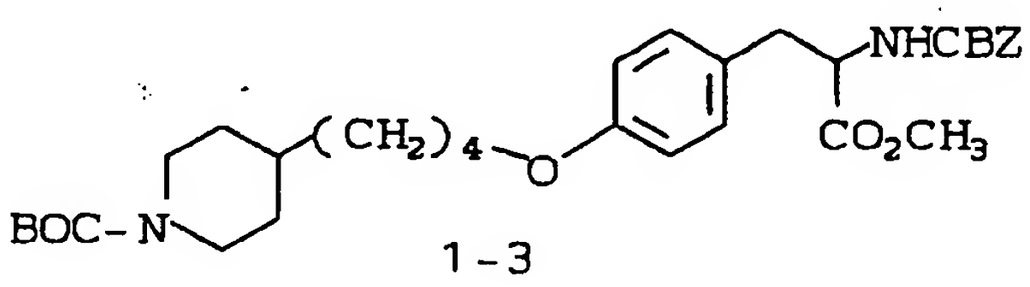
1-2

2-S-(Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-2)

N-CBZ-L-tyrosine (1-1) (17.58 g, 0.055 mmole) was dissolved in DMF (75 mL), cooled to 0-10° C and treated with sodium hydride (2.88 g, 0.12 mole). This suspension was stirred at 0-10° C for 1 hour and then N-t-butyloxycarbonylpiperidin-4-ylbutyl bromide (17.70 g, 0.055 mole) in 25 mL DMF was added dropwise over 15 minutes. The reaction mixture was then stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was taken up in a mixture of 500 mL EtOAc/100 mL 10% $KHSO_4$. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent was removed to give a viscous oil. This was purified by flash chromatography on silica gel eluting with 98:2:0.5 $CHCl_3/CH_3OH$/HOAc to give pure 1-2 (23.75 g), R_f = 0.35, as a pale yellow oil.

^1H NMR (300MHz, $CDCl_3$) δ 1.00-1.15 (2H, m), 1.20-1.80 (16H, m), 2.62 (2H, t), 3.10 (2H, m), 3.91 (2H, t), 4.04 (2H, m), 5.10 (2H, m), 5.22 (1H, d), 6.78 (2, d), 7.04 (2H, d), 7.35 (5H, m).

EXAMPLE 2



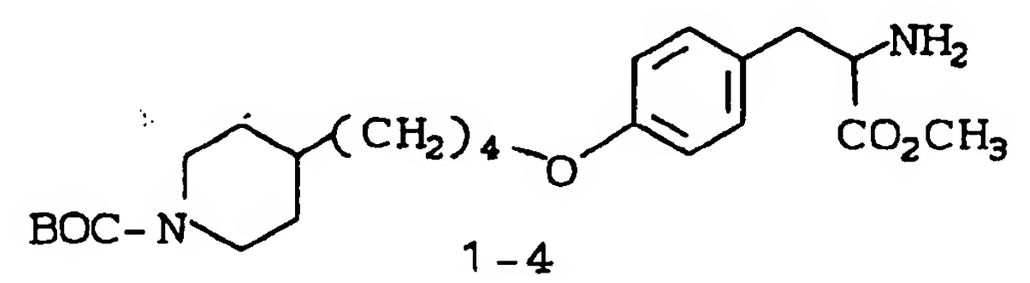
1-3

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-3)

1-2 (10.05 g, 18.1 mmole) was dissolved in CH_3OH (150 mL) at room temperature and cesium carbonate (2.95 g, 9.06 mmole) was added and the resulting mixture stirred for 15 minutes to give a clear solution. The CH_3OH was removed at reduced pressure and the residue was then dissolved in DMF (150 mL) and treated dropwise with methyl iodide (2.57), 18.1 mmole). The resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was taken up in 400 mL ether and washed with 3 x 50 mL portions of H_2O, 50 mL brine and dried (Na_2SO_4). Solvent removal provided 1-3 as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.0-1.15 (2H, m), 1.30-1.70 (16H, m), 2.68 (2H, dt), 3.05 (2H, m), 3.72 (3H, s), 3.91 (2H, t), 4.08 (2H, d), 4.61 (1H, m), 5.10 (2H, m), 5.18 (1H, m), 6.79 (2H, d), 6.98 (2H, d), 7.35 (5H, m).

EXAMPLE 3



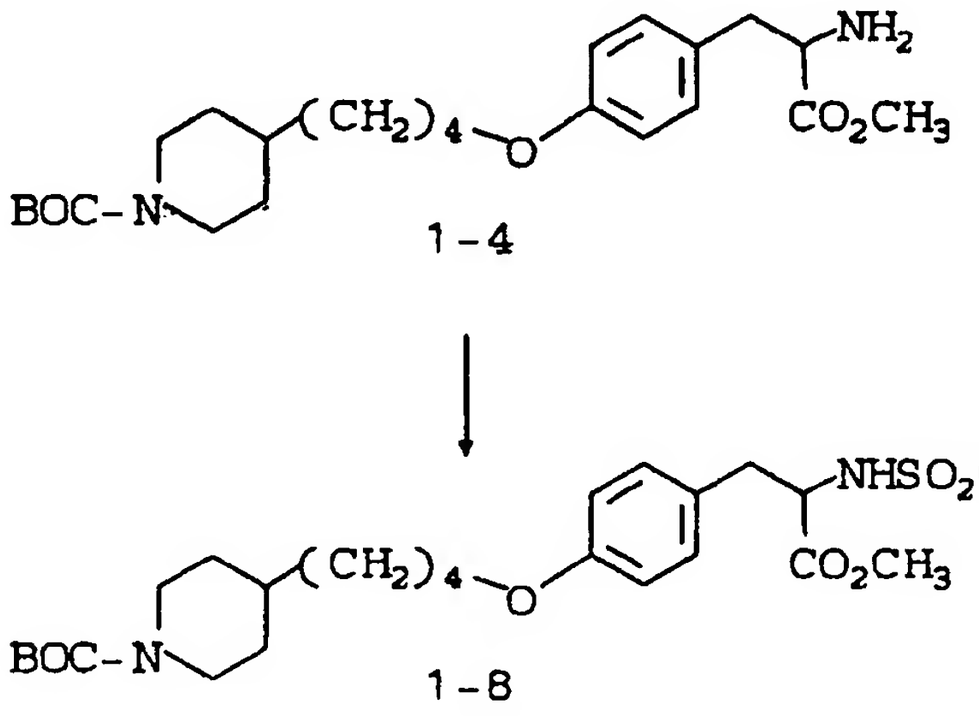
1-4

Methyl 2-S-Amino-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)-butyloxyphenyl]propionate (1-4)

To 1-3 (5.0 g, 8.79 mmole) dissolved in absolute ethanol (150 mL) was added 10% Pd/C (0.5 g) and the

resulting suspension was hydrogenated under balloon pressure for 12 hours. The catalyst was then filtered off and the solvent was removed in vacuo to give 1-4 (3.6 g) as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.20 (2H, m), 1.22-1.55 (12H, m), 1.60-1.75 (4H, m), 2.00 (2H, bs), 2.68 (2H, t), 2.87 (1H, dd), 3.05 (1H, dd), 3.72 (3H, s), 3.93 (2H, t), 4.09 (2H, m), 6.82 (2H, d), 7.10 (2H, d).

EXAMPLE 4



Methyl 2-S-(n-Butylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-8)

1-4 (0.59 g, 1.36 mmole) was dissolved in ethyl acetate (10 mL) and $NaHCO_3$ (0.7 g, 8.68 mmole) was added with stirring at room temperature followed by butanesulfonyl chloride (0.36 mL, 2.76 mmole) and the resulting mixture was refluxed for 26 hours. The cooled reaction mixture was filtered and concentrated and the residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give pure 1-8 (0.305 g) R_f = 0.7 in 1:1 hexane/EtOAc, ninhydrin stain.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, t), 1.05 (2H, ddd), 1.45 (9H, s), 1.1-1.6 (1H, m), 1.7 (4H, m), 2.6 (2H, t), 2.6-2.8 (2H, m), 2.78 (1H, dd), 3.05 (1H, dd), 3.7 (3H, s), 3.93 (2H, t), 4.05 (2H, bd), 4.15 (1H, dd), 6.85 (2H, d), 7.15 (2H,d).

EXAMPLE 5

2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-9)

1-8 (0.325 g, 0.59 mmole) was dissolved in 1:1:1 CH_3OH/H_2O/THF and $LiOH•H_2O$ (0.157g, 3.76 mmole) was added. The resulting solution was stirred at room temperature for 3 hours, then concentrated, diluted with 10% $KHSO_4$ and extracted with EtOAc. This provided 2-S-(n-butylsulfonylamino)-3[4-(N-t-butyloxycarbonyl-piperidin-4-yl)butyloxyphenyl]propionic acid. This acid (0.315 g, 0.59 mmole) was dissolved in EtOAc (20 mL) and treated with HCl gas at -20° C for 15 minutes. The reaction mixture was then stoppered and was stirred

at -5° C for 1 hour at which time all starting material was consumed. Argon gas was bubbled through the reaction mixture for 15 minutes and the solvent was removed to give a residue that was triturated with ether to provide pure 1-9 (0.29 g) as a pale yellow solid.

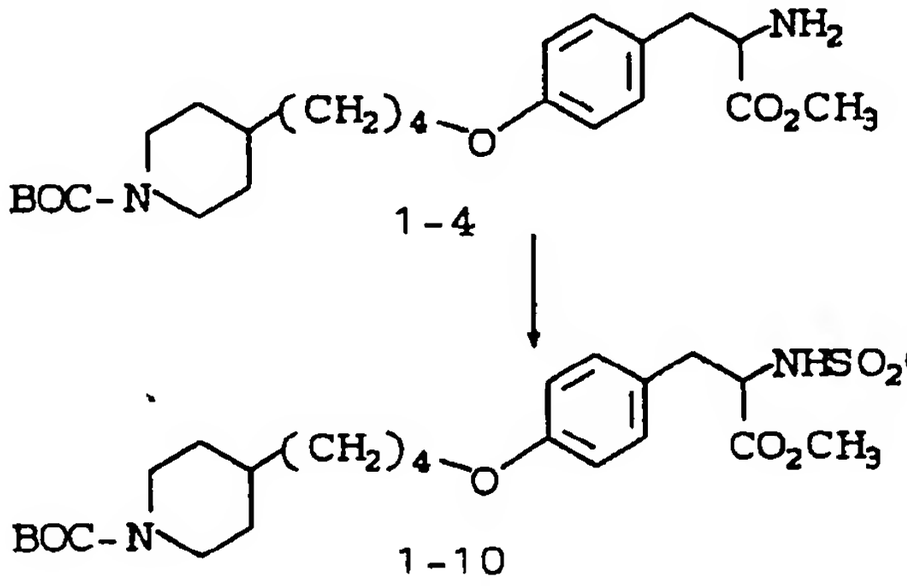
^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (3H,t), 1.2 (2H,dd), 1.2-1.7 (9H,m), 1.7 (2H, m), 1.95 (2H, bs), 2.65 (2H, t), 2.8 (1H, dd), 2.95 (2H, bt), 3.10 (1H, dd), 3.83 (2H, bs), 3.95 (2H, t), 4.1 (1H, dd), 6.85 (2H, d), 7.2 (2H, d).

Analysis for $C_{22}H_{38}N_2O_5$IS•HCl•0.8 H_2O

Calculated: C = 53.76, H = 7.92, N = 5.70

Found: C = 53.76, H = 7.66, N = 5.44.

EXAMPLE 6

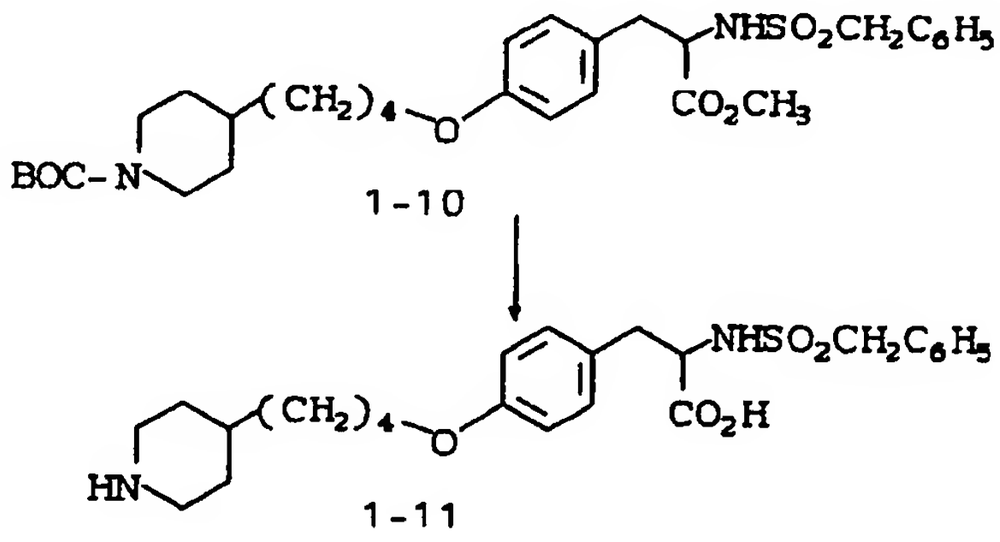


Methyl 2-S-(Benzylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-10)

1-4 (0.59g, 1.36 mmole) was treated with benzylsulfonyl chloride (0.263 g, 1.38 mmole) as described above for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 3:1 hexane/EtOAc to give pure 1-10 (0.35 g) as an oil.

^{1}H NMR (300 MHz, CD_3OD) δ 0.85-1.10 (2H, m), 1.10-1.23 (2H,m), 1.35-1.52 (11H, m), 1.61-1.80 (4H, m), 2.65-3.00 (4H, m), 3.65 (3H, s), 3.90-4.14 (5H, m), 6.85 (2H, d), 7.08 (2H, d), 7.22 (2H, m), 7.30 (3H, m).

EXAMPLE 7



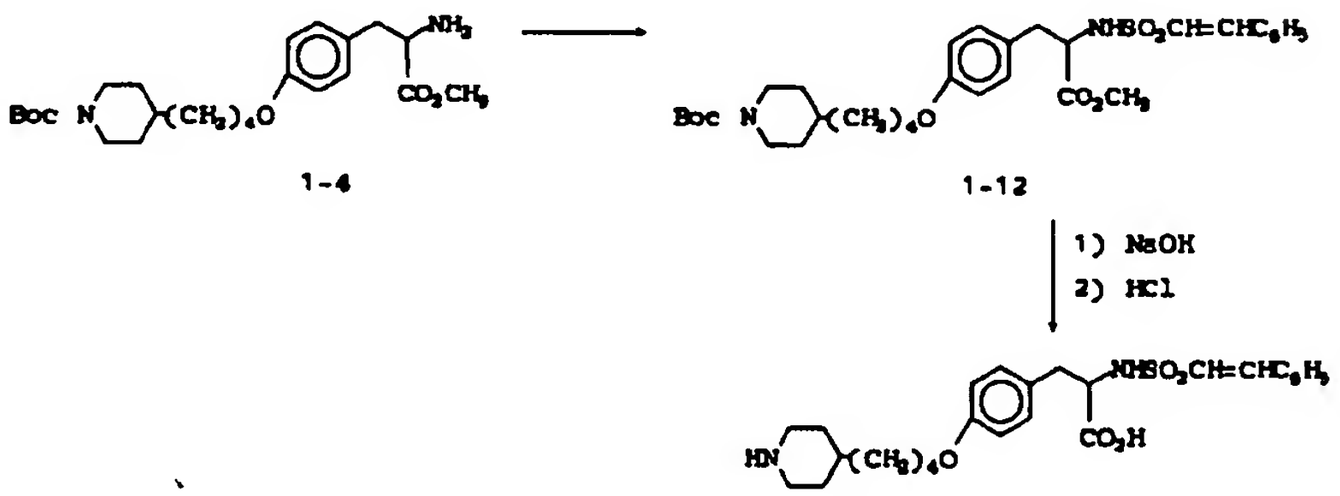
2-S-(Benzylsulfonylamino)-3-[4-(piperidin-4-yl)butyl-oxyphenyl]propionic acid hydrochloride (1-11)

Treatment of 1-10 (0.354 g, 0.60 mmole) with liOH (0.15 g, 3.7 mmole) as described for 1-8 gave 2-S-(benzylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (0.35 g) as a viscous oil.

^{1}H NMR (300MHz CD_3OD) δ 0.84-1.06 (3H, m), 1.23 (4H, m), 1.34-1.50 (11H, m), 1.60-1.78 (5H, m), 2.65 (2H, bt), 2.82 (1H, m), 3.02 (1H, m), 3.91 (2H, m), 3.96-4.12 (5H, m), 6.83 (2H, d), 7.15 (2H, d), 7.22 (2H, m), 7.29 (3H, m).

This acid (0.35 g, 0.60 mmole) was dissolved in 20 mL EtOAc and treated with HC1 gas as described for

1-9 to give pure 1-11 as a white solid (0.30 g).
^{1}H NMR (300MHz, CD_3OD) δ 1.32 (4H, m), 1.40-1.65 (3H, m), 1.72 (2H, m), 1.92 (2H, d), 2.77-3.08 (4H, m), 3.33 (3H, m), 3.95-4.14 (5H, m), 6.86 (2H, d), 7.17 (2H, d), 7.28 (2H, m), 7.31 (3H, m).



Methyl 2-S-(2-Styrylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-12)

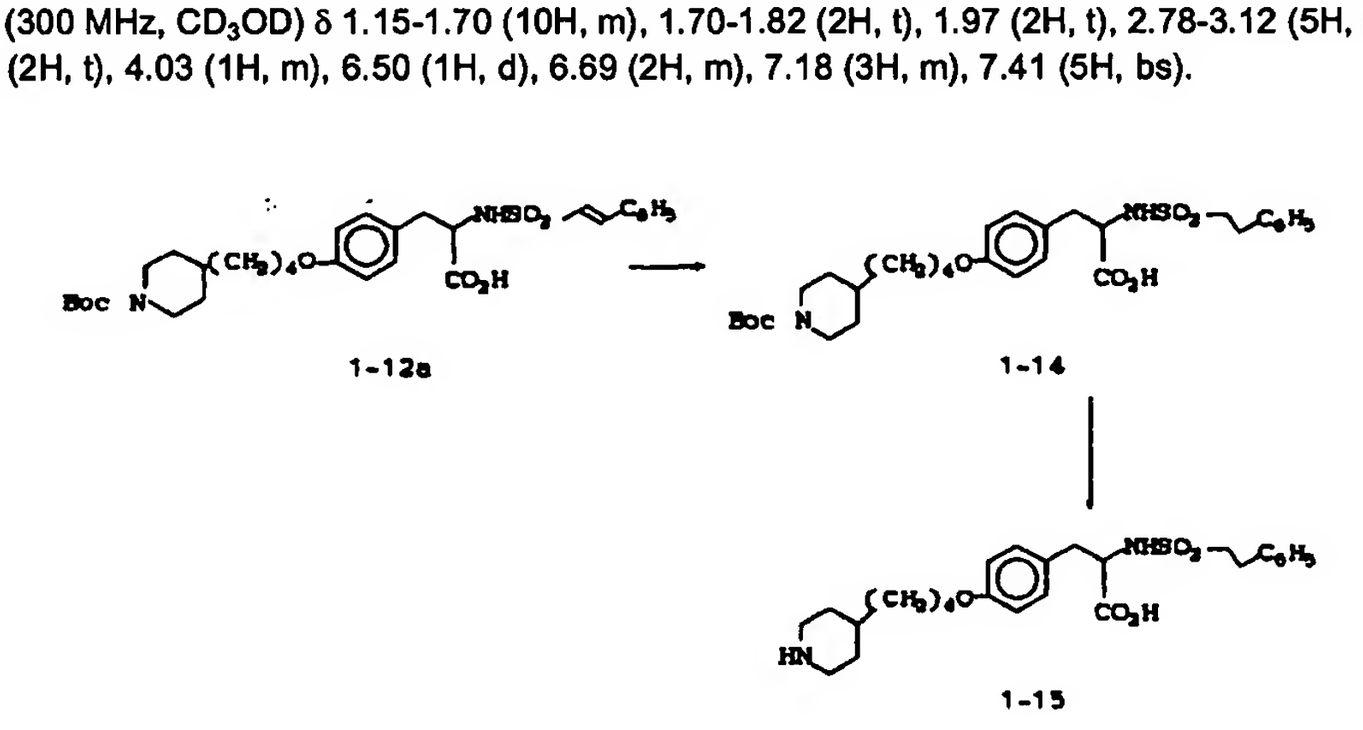
1-4 (0.647 g, 15 mmoles) was dissolved in ethyl acetate (20 ml), and $NaHCO_3$ (0.454 g, 5.4 mmoles) was added followed by β-styrenesulfonyl chloride (0.365 g, 18.0 mmoles) and the resulting reaction mixture was heated at reflux with stirring for 16 hours. The cooled reaction mixture was filtered, the solvent removed and the residue was purified by flash chromatography on silica gel eluting with hexane (3)/ethyl acetate (1) to give pure 1-12.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.30-1.55 (14 H, m), 1.65-1.80 (4H, m), 2.68 (2H, t), 3.01 (2H, dt), 3.62 (3H, s), 3.88 (2H, t), 4.09 (2H, m), 4.22 (1H, m), 4.98 (1H, d), 6.45 (1H, d), 6.80 (2H, d), 7.06 (2H, d), 7.40 (4H, s).

2-S-(2-Styrylsulfonylamino)-3-4-[4-piperidinylbutyloxyphenyl)propionic acid hydrochloride (1-13)

1-12 (0.58 g, 0.97 mmole) was dissolved in THF(1)-H_2O(1)-MeOH(1) (15 ml) and lithium hydroxide (0.12 g, 5.0 mmole) was added and the resulting clear solution was stirred overnight at room temperature.

The reaction mixture was diluted with 75 ml H_2O, acidfied to pH 2-3 with 10% $KHSO_4$ solution and then extracted with 3 x 50 ml EtOAc. The organic extract was dried, the solvent removed, and the residue purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-MeOH(3)-HOAc(1) to give the desired acid (R_f=0.2).

This acid was dissolved in EtOAc and treated with HCl gas as described for 1-9 to give 1-13.
^{1}H NMR (300 MHz, CD_3OD) δ 1.15-1.70 (10H, m), 1.70-1.82 (2H, t), 1.97 (2H, t), 2.78-3.12 (5H, m), 3.35 (3H, m), 3.87 (2H, t), 4.03 (1H, m), 6.50 (1H, d), 6.69 (2H, m), 7.18 (3H, m), 7.41 (5H, bs).



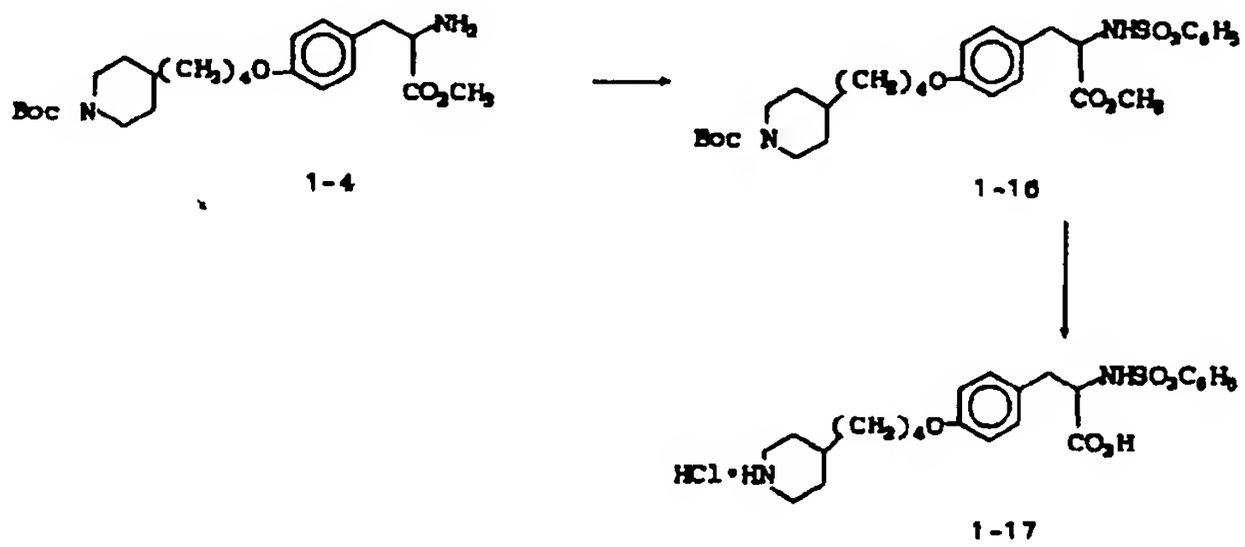
2-S-(2-Phenethylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-14)

1-12a (0.21 g) was dissolved in 20 ml absolute ethanol, 0.1 g 10% Pd/C was added and the stirred sus-

pension was hydrogenated under balloon pressure. After 4 hours the reaction was stopped and the solvent was removed to give the desired product 1-14 (0.194 g).
^{1}H NMR (300 MHz, CD_3OD) δ 1.05 (2H, m), 1.30-1.40 (3H, m), 1.47 (14H, m), 1.72 (5H, m), 2.67-2.93 (8H, m), 3.13 (1H, m), 3.31 (2H, m), 3.82 (2H, m), 4.00-4.20 (4H, m), 6.82 (2H, d), 7.07 (2H, d), 7.21 (5H, m).

2-S-(2-Phenethylsulfonylamino)-3-4-[4-piperidinylbutyloxyphenyl]propionic acid hydrochloride (1-15)

1-14 (0.194 g) was dissolved in EtOAc and treated with HCl gas as described for 1-9 to provide pure 1-15 (0.145 g).
^{1}H NMR (300 MHz, CD_3OD) δ 1.25-1.68 (8H, m), 1.73 (2H, m), 1.93 (2H, m), 2.78 (3H, m), 2.91 (4H, m), 3.13 (1H, m), 3.33 (4H, m), 3.86 (2H, m), 4.18 (1H, m), 6.80 (2H, d), 7.09 (2H, d), 7.22 (5H, m).

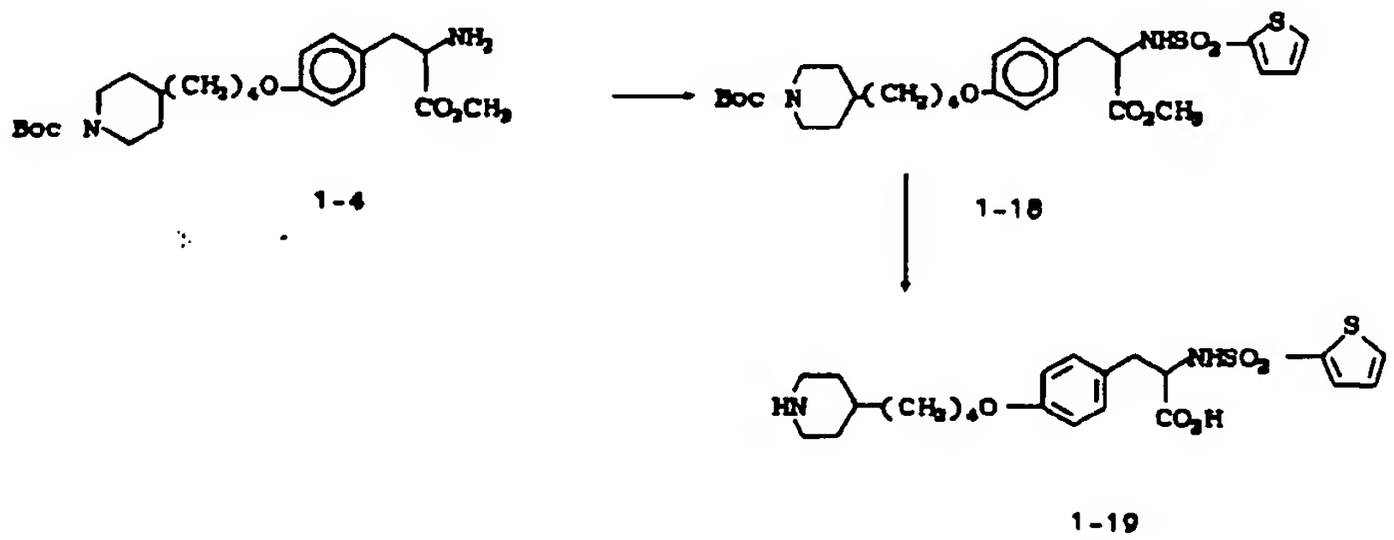


Methyl 2-S-(Phenylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-16).

1-4 (0.647 g, 1.5 mmoles) was treated with phenylsulfonyl chloride (0.318 g, 1.8 mmoles) as described for 1-8. The crude product was purified by flash chromatography on silica gel eluting with $CHCl_3$(98)-MeOH(2) to give pure 1-16 (0.67 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (2H, m), 1.25-1.40 (3H, m), 1.42 (9H, bs), 1.60-1.85 (6H, m), 2.66 (2H, m), 2.96 (2H, d), 3.55 (3H, s), 3.89 (2H, t), 4.09 (4H, m), 5.12 (1H, d), 6.72 (2H, d), 6.95 (2H, d), 7.40-7.65 (3H, m), 7.75 (2H, m).

2-S-(Phenylsulfonylamino)-3-(4-piperidin-4-ylbutyloxyphenyl)propionic acid hydrochloride (1-17).

1-16 (0.525 g) was treated with lithium hydroxide as described for 1-8 to give crude product that was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-MeOH(3)-HOAc(1) to provide pure acid (R_f = 0.2).
This acid was treated with HCl gas in EtOAc as described for 1-9 to provide pure 1-17.
^{1}H NMR (300 MHz, CD_3OD) δ 1.28-1.47 (6H, m), 1.50-1.70 (3H, m), 1.75 (2H, m), 1.97 (2H, d), 2.77 (1H, m), 2.95 (3H, m), 3.35 (4H, m), 3.93 (3H, m), 6.72 (2H, d), 7.02 (2H, d), 7.41 (2H, m), 7.52 (1H, m), 7.67 (2H, m).



Methyl 2-S-(2-Thienylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate

(1-18).

1-4 (0.304 g, 0.7 mmoles) was treated with 2-thienylsulfonyl chloride (0.155 g, 0.85 mmoles) as described for 1-8 to provide crude product. This was purified by flash chromatography on silica gel eluting with $CHCl_3$(98)-CH_3OH(2) to afford pure 1-18 as a viscous oil, R_f 0.3 [silica gel, $CHCl_3$(98)-CH_3OH(2)]

^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.31 (4H, m), 1.36-1.80 (16 H, m), 2.68 (2H, bt), 3.03 (2H, d), 3.57 (3H, s), 3.91 (2H, t), 4.08 (2H, m), 4.29 (1H, m), 5.16 (1H, d), 6.78 (2H, d), 7.00 (4H, m), 7.55 (2H, dd).

2-S-(2-Thienylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-19).

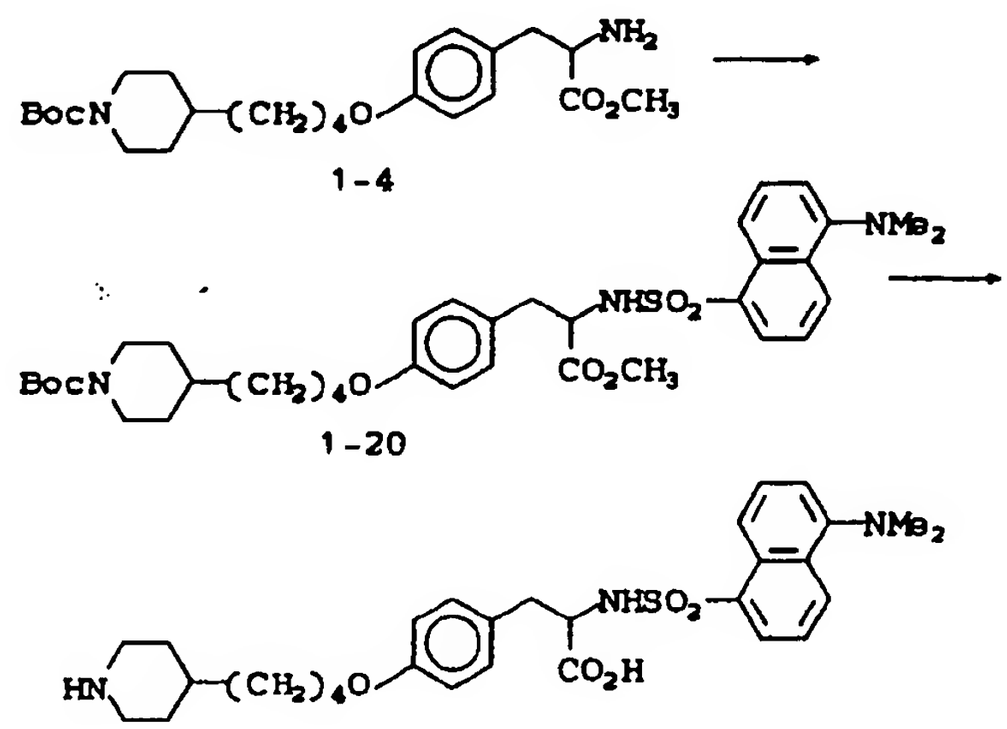
Treatment of 1-18 (0.22 g, 0.38 mmoles) with LiOH (0.045 g, 1.89 mmoles) as described for 1-8 provided the desired acid, which was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-CH_3OH(3)-HOAc(1).

^1H NMR (300 MHz, CD_3OD) δ 1.05 (2H, d t), 1.20-1.40 (5H, m), 1.40-1.60 (12H, m) 1.65-1.80 (5H, m), 2.65-2.82 (4H, m), 2.98 (1H, dd), 3.30 (1H, m), 3.92 (2H, t), 4.00-4.13 (5H, m), 6.75 (2H, d), 7.02 (3H, m), 7.39 (1H, d), 7.67 (1H, d).

Treatment of this acid with HCl gas as described for 1-9 provided 1-19 as a white solid after trituration.

Analysis Calcd. for $C_{22}H_{30}N_2O_5S_2 \bullet HCl \bullet 0.5\ H_2O$:
C, 51.60, H, 6.30, N, 5.47.
Found: C, 51.57, H, 6.20, N, 5.51.

^1H NMR (300 MHz, CD_3OD) δ 1.29-1.45 (4H, m), 1.47-1.70 (3H, m), 1.71-1.83 (2H, m), 1.91-2.00 (2H, bd), 2.79 (1H, m), 2.90-3.04 (3H, m), 3.95 (2H, t), 4.04 (1H, m), 6.76 (2H, d), 7.05 (3H, m), 7.40 (1H, m), 7.79 (1H, m).



1-21

2-S-(Dansylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-20).

1-4 (0.304 g, 0.7 mmoles) was treated with dansyl chloride (0.208 g, 0.77 mmoles) as described for 1-8 to provide crude product which was purified by flash chromatography on silica gel eluting with hexane(75)-EtOAc(25) to give pure 1-20. R_f 0.25 (silica gel eluting with hexane(75)-EtOAc(25).

^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.21-1.38 (6H, m), 1.40-1.53 (11H, m), 1.60-1.80 (6H, m), 2.68 (2H, bt), 2.89 (6H, s), 3.33 (2H, s), 3.89 (2H, t), 4.05-4.19 (4H, m), 5.24 (1H, m), 6.62 (2H, d), 6.82 (2H, d), 7.18 (1H, d), 7.50 (2H, m), 8.19 (2H, t), 8.51 (1H, d).

2-S-(Dansylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-21).

Treatment of 1-20 (0.275 g, 0.412 mmoles) with LiOH as described for 1-8 gave the desired acid as a highly fluorescent viscous residue.

^{1}H NMR (300 MHz, CD_3OD) δ 1.09 (2H, m), 1.22-1.40 (3H, m), 1.40-1.57 (12H, m), 1.65-1.80 (3H, m), 2.60-2.80 (3H, m), 2.90 (6H, s), 3.31 (3H, m), 3.80 (2H, t), 3.90 (1H, m), 4.01-4.15 (4H, m), 6.47 (2H, d), 7.21 (1H, d), 7.42 (2H, m), 7.98 (1H, d), 8.20 (1H, d), 8.46 (1H, d).

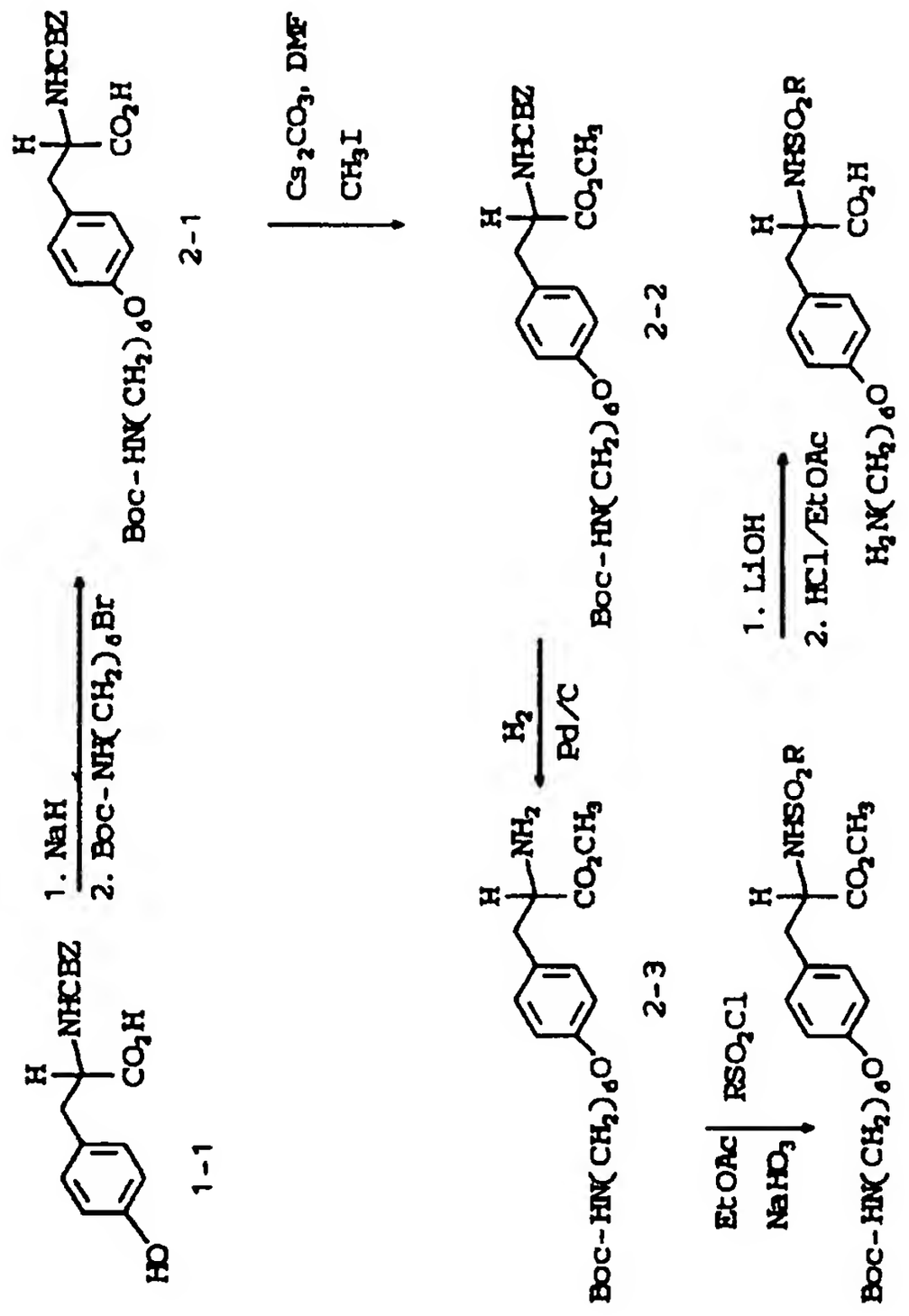
Treatment of this acid in EtOAc with HCl gas as described for 1-9 provided 1-21 as a white solid upon ethylacetate trituration.

Analysis for $C_{30}H_{39}N_3O_5S \cdot 1.8\ HCl \cdot H_2O$:

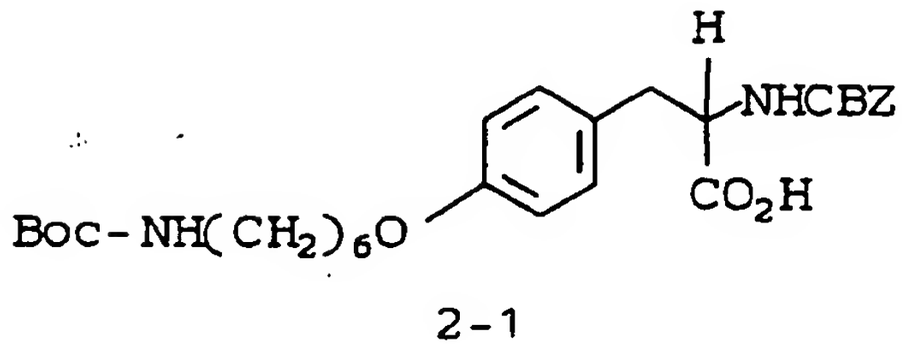
	C, 56.53; H, 6.77; N, 6.59; Cl, 10.01.
Found:	C, 56.48; H, 6.66; N, 6.36; Cl, 10.21.

^{1}H NMR (300 MHz, CD_3OD) δ 1.30-1.51 (7H, m), 1.52-1.80 (4H, m), 1.95 (2H, bt), 2.65 (1H, m), 2.95 (3H, m), 3.30-3.40 (4H, m), 3.45 (6H, s), 3.84-3.97 (3H, m), 6.45 (2H, d), 6.77 (2H, d), 7.71 (2H, m), 8.00 (1H, d), 8.16 (2H, d), 8.55 (1H, d), 8.70 (1H, d).

SCHEME 2


1-1
1. NaH
2. Boc-NH(CH2)6Br
Boc-HN(CH2)6O
2-1
Cs2CO3, DMF
CH3I
2-2
H2
Pd/C
2-3
EtOAc
NaHCO3
RSO2Cl
1. LiOH
2. HCl/EtOAc
H2N(CH2)6O

EXAMPLE 8



2-1

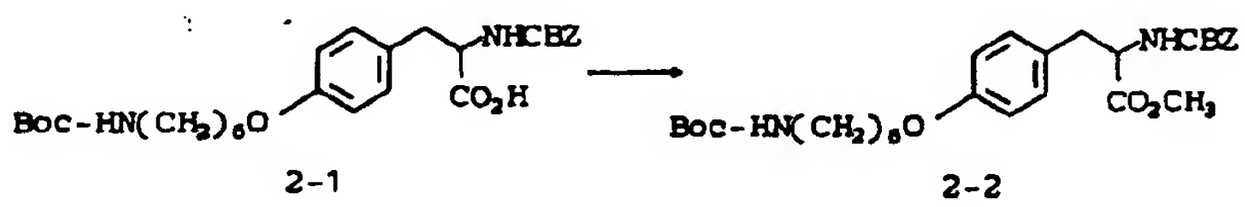
2-S-(Benzyloxycarbonylamino)-3-[4-(6-N-t-butyloxycarboxylaminohexyloxy)phenyl]propionic acid (2-1)

N-CBZ-L-tyrosine (15.0 g, 0.045 mole) was dissolved in 75 mL DMF and added at 0-10° C to a suspension of sodium hydride (2.16 g, 0.09 mole) in 25 mL DMF. The resulting suspension was stirred at 0-10° C for 1.0 hour and then 6-(t-butyloxycarbonylamino)hexyl bromide (12.6 g, 0.045 mole) in 25 mL DMF was added dropwise at 0-5° C and the clear, dark reaction mixture was stirred at room temperature overnight.

After solvent removal, the residue was taken up in EtOAc and this was made acidic with 10% $KHSO_4$ solution. The organic phase was separated, washed with brine, dried (Na_2SO_4) and the solvent removed to give an oil. This was purified by column chromatography on silica gel eluting with 98:2:1 $CHCl_3/CH_3OH/HOAc$ to give pure 2-1 as a clear oil.

^1H NMR (300 MHz, CD_3OD) δ 1.45 (15H, m), 1.75(2H, m), 2.80-3.15 (6H, m), 3.91(2H, t), 4.38(1H, m), 4.95(6H, m), 6.85(2H,d), 7.06(2H,d)

EXAMPLE 9



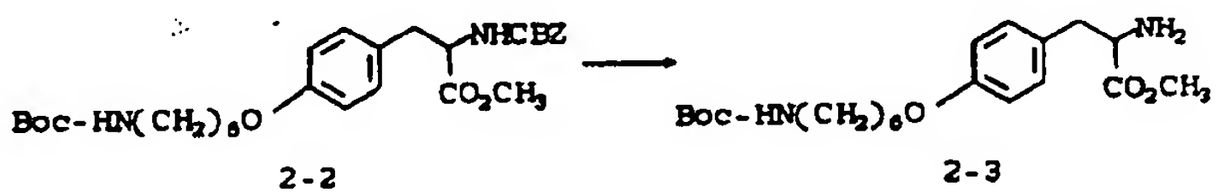
2-1 2-2

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-2)

Compound 2-1 (10.0 g, 19.43 mmole) in 75 mL DMF was treated with cesium carbonate (3.16 g, 9.72 mmole) with stirring at room temperature for 1.9 hours. Then, methyl iodide (2.76 g, 19.43 mmole) was added dropwise and the reaction mixture was stirred overnight at ambient temperature. The solvent was removed at high vacuum (30° C) and the residue was taken up in 300 mL EtOAc and washed with 2 x 40 mL protions of saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Solvent removal provided 2-2 (8.5 g, 83%) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 1.25-1.53 (16H, m), 1.76 (2H, m), 2.96-3.17 (4H, m), 3.71 (3H, s), 3.90 (2H, t), 4.61 (1H, m), 5.10 (2H, m), 5.19 (1H, m), 6.88 (2H, d), 6.98 (2H, d), 7.32 (5H, m).

EXAMPLE 10



2-2 2-3

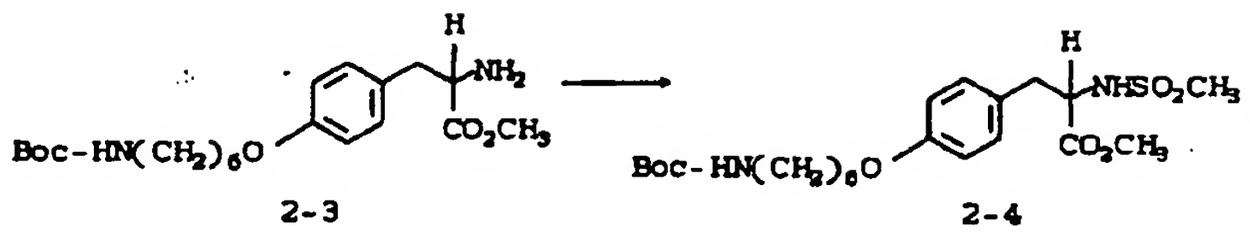
Methyl 2-S-Amino-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-3)

Compound 2-2 (8.0 g, 15.1 mmole) was dissolved in 150 mL absolute ethanol and 1.0 g 10% Pd/ C was added. This suspension was hydrogenated in a Parr apparatus (50 psi) for 3.5 hours. The catalyst was then filtered off and the solvent removed on the rotary evaporator to give pure 2-3 (5.56 g) as a clear oil. R_f = 0.4 on SiO_2 with 95:5 $CHCl_3/CH_3OH$

^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.55 (16H, m), 1.70 (2H, m), 2.80 (1H, m), 3.00-3.17 (3H, m), 3.71 (3H, s),

3.93 (2H, t), 6.82 (2H, d), 7.09 (2H,d).

EXAMPLE 11

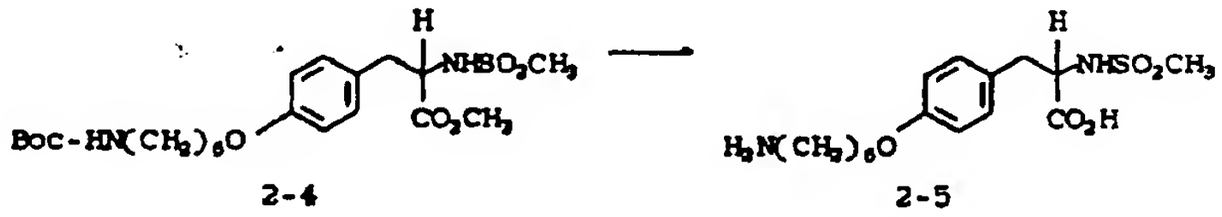


2-S-(Methylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-4)

2-3 (0.40 g, 1.01 mmole) was treated with methanesulfonyl chloride (0.116 g, 1.01 mmole) and $NaHCO_3$ (0.25 g, 3.0 mmole) as described for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 30% EtOAc /hexanes to give pure 2-4 (0.10g) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 1.36-1.56 (15H, m), 1.77 (2H, m), 2.70 (3H, s), 3.78 (3H, s), 3.92 (2H, t), 4.36 (1H, m), 4.90 (1H, d). 6.82 (2H, d), 7.09 (2H, d).

EXAMPLE 12



2-S-(Methylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-5)

2-4 (0.1 g, 0.212.mmole) was treated with LiOH (0.026 g, 1.06 mmole) as described for 1-8 to provide 2-S-(methylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.125g) as a viscous oil.

^1H NMR (300 MHz, CD_3OD) δ 1.30-1.55 (16H, m), 1.75 (2H, m), 2.63 (3H, s), 2.85 (1H, dd), 3.0-3.13 (3H, m), 3.93 (2H, t), 4.17 (1H, m), 6.83 (2H, d), 7.20 (2H, d).

This acid was dissolved in EtOAc (20 mL) and treated with HCl gas as described for 1-9. Solvent removal provided a residue that was triturated with 30 mL Et_2O to provide pure 2-5 as a white solid (0.09 g).

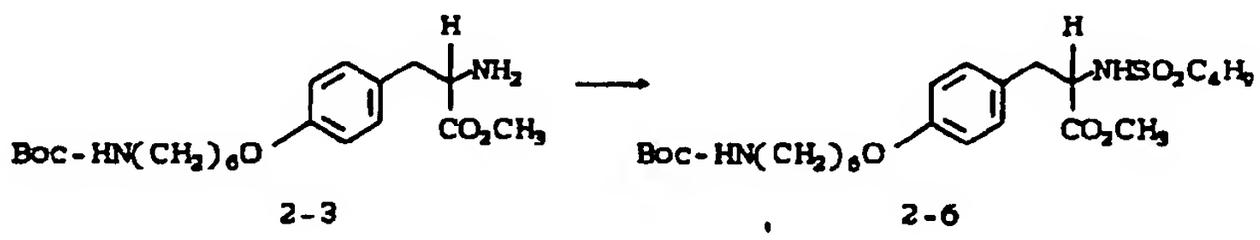
^1H NMR (300MHz, CD_3OD), δ 1.40-1.60 (4H, m), 1.60 (2H, m), 1.69 (2H, m), 2.68 (3H, s), 2.82 (1H, dd), 2.92 (2H, t), 3.10 (1H, dd), 3.30 (2H, m), 3.97 (2H, t), 4.18 (1H, m), 6.83 (2H, d), 7.19 (2H, d).

Analysis for $C_{16}H_{26}N_2O_5S.HCl.0.25\ H_2O$

Calculated: C = 48.11, H = 6.94, N = 7.01

Found: C = 48.16, H = 6.82, N = 6.98.

EXAMPLE 13

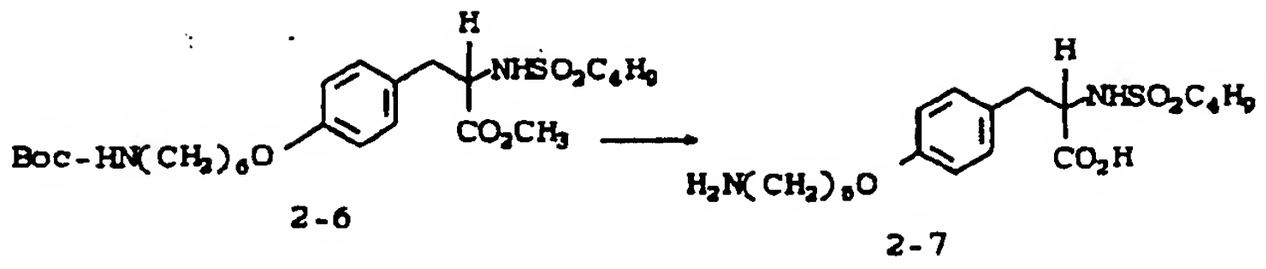


Methyl 2-S-(Butylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-6)

2-3 (0.40 g, 1.01 mmole) was treated with butylsulfonyl chloride (0.47 g, 3.03 mmole) and $NaHCO_3$ (0.50 g, 6.0 mmole) as described for 1-8. Crude reaction product was purified by flash chromatography on silica gel eluting with 30% EtOAc/hexanes to give pure 2-6 (0.22 g) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 0.87 (3H, t), 1.35-1.54 (18 H, m), 1.61 (2H, m), 1.77 (2H, m), 2.74 (2H, t), 2.95 (1H, dd), 3.05-3.18 (3H, M), 3.90 (2H, t), 4.32 (1H, m), 4.72 (1H, m), 6.82 (2H, d), 7.07 (2H, d).

EXAMPLE 14



2-S-(Butylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-7)

2-6 (0.2 g, 0.39 mmole) was treated in THF (1)/H_2O (1)/CH_3OH(1) solution with LiOH (0.05g, 2.12 mmole) as described for 1-8 to provide 2-S-(butylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.235 g) as a viscous oil.

^1H NMR (300 MHz, CD_3OD) δ 0.83 (3H, t), 1.35-1.56 (16H, m) 1.76 (2H, m), 2.61 (2H, t), 2.79 (1H, ddd), 3.00-3.14 (3H, m), 3.92 (2H, t), 4.11 (1H, m), 6.82 (2H, d), 7.18 (2H, d).

This acid (0.235 g, 0.7 mmole) was dissolved in EtOAc (30 mL) and treated with HCl gas as described for 1-9. The residue was triturated with a solution of ether (40 mL)/EtOAc (10mL) to provide 2-7 (0.17g) as a white solid.

^1H NMR (300MHz, CD_3OD) δ 0.85 (3H, t), 1.24 (2H, m), 1.35-1.60 (6H, m), 1.70 (2H, m), 1.80 (2H, m), 2.66 (2H, t), 2.78 (1H, dd), 2.92 (2H, t), 3.10 (1H, dd), 3.30 (1H, m), 6.85 (2H, d), 7.20 (2H, d).

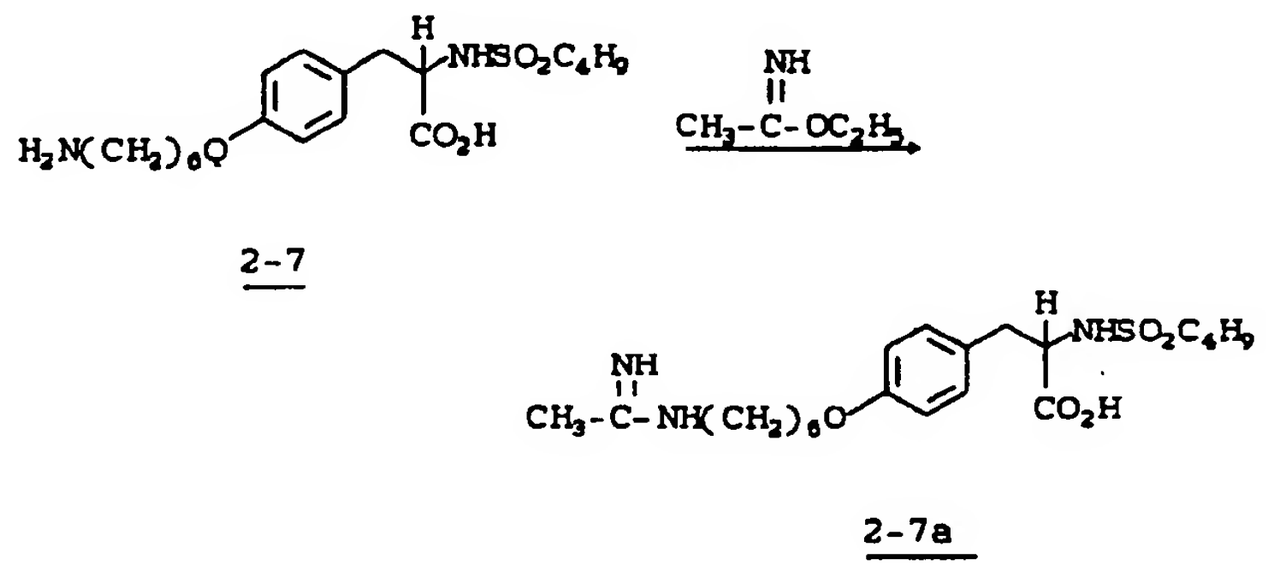
Analysis for $C_{19}H_{32}N_2O_5S.HCl$

Calculated: C = 52.22, H = 7.61, N = 6.41

Found: C = 51.80, H = 7.61, N = 6.33.

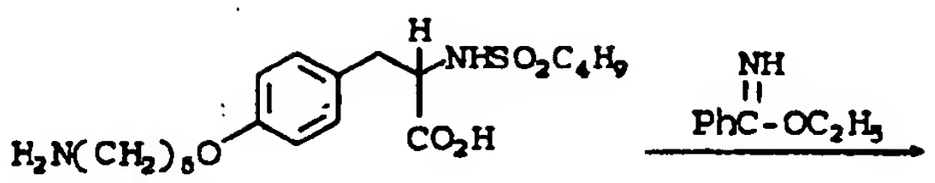
EXAMPLE 14A

2-S-(Butylsulfonylamino)-3-[4-(6-acetamidinohexyloxy)phenyl]propionic acid (2-7a)

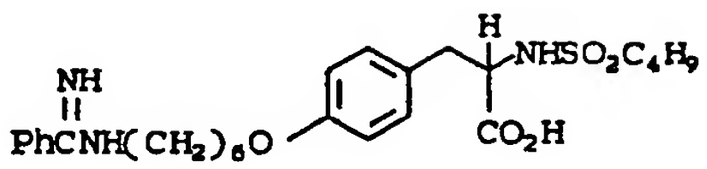


A solution of 2-7 (1.0 g, 2.29 mmole) in THF (30 ml) is treated with ethyl acetimidate (0.2 g, 2.29 mmol) and the resulting reaction mixture is stirred at room temperature for 16 hours. The solvent is then removed and the residue is recrystallized from ethyl acetate to give pure 2-7a.

EXAMPLE 14B



2-7

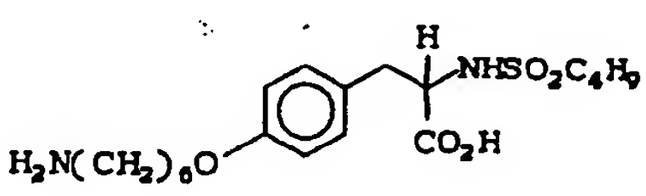


2-7b

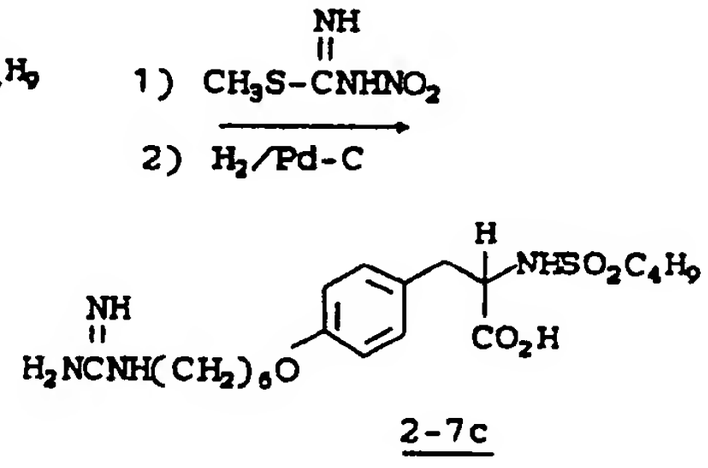
2-S-(Butylsulfonylamino)-3-[4-(6-benzamidinohexyloxy)phenyl]propionic acid (2-7b)

A solution of 2-7 (1.0 g, 2.29 mmole) in THF (30 ml) is treated with ethyl benzimidate (0.34 g, 2.29 mmole) and the resulting solution is stirred at room temperature for 20 hrs. The solvent is removed and the residue is taken up in EtOAc, filtered and recystallized to give pure 2-7b.

EXAMPLE 14C



2-7



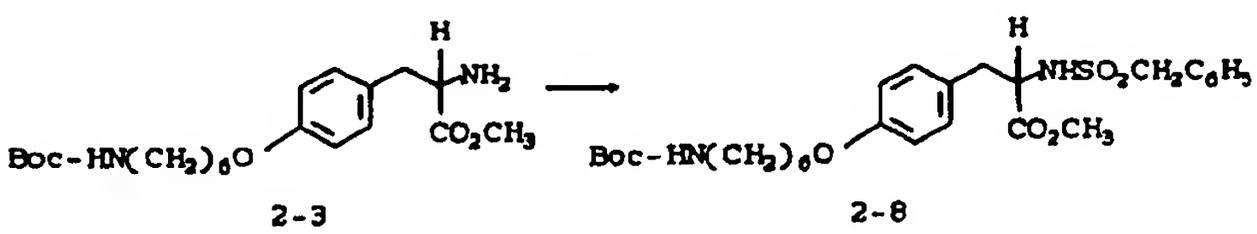
2-7c

2-S-(Butylsulfonylamino)-3-[4-(6-guanidinohexyloxyphenyl]propionic acid (2-7c)

A mixture of 2-7 (1.0 g, 2.29 mmol) and N-nitrosomethylthioguanidine (0.32 g, 2.29 mmol) is heated at 40° for 5 minutes in absolute EtOH (15 ml) and then is allowed to stand for 1 day at room temperature. The solvent is removed in vacuo and the residue is purified by flash chromatography on silica eluting with $CHCl_3$(95)-CH_3OH(5)-HOAc(2) to give the desired nitroguanidino intermediate.

This is dissolved in 10% HCl-CH_3OH (20 ml) and shaken in a Parr apparatus (50 psi) in the presence of 10% Pd-C (100 mg) at room temperature for 8 hours. The catalyst is then removed by filtration, the solvent is removed in vacuo, and the residue dissolved in 10% aqueous HCl solution and heated at reflux for 2 hours. The solvent is removed in vacuo and the residue purified by chromatography on a Dowex 1-X2 column eluting with water to give pure 2-7c.

EXAMPLE 15

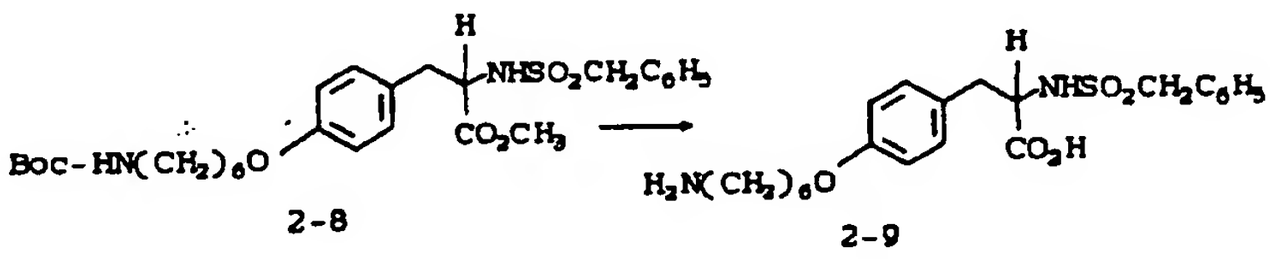


2-3 2-8

Methyl 2-S-(Benzylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-8)

2-3 (0.29 g, 0.735 mmole) was treated with benzylsulfonyl chloride (0.14 g, 0.735 mmole) and $NaHCO_3$ (0.185 g, 2.2 mmole) as described for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 1:1 hexanes/EtOAc to give pure 2-8 (0.27 g) as a clear oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.47-1.69 (15H, m), 1.90 (2H, m), 2.18 (2H, s), 3.08 (2H, d), 3.25 (2H, m), 3.85 (3H, s), 4.05 (2H, t), 4.19-4.20 (4H, m), 4.80 (1H, d), 6.83 (2H, d), 7.12 (2H, d), 7.47 (5H, m).

EXAMPLE 16

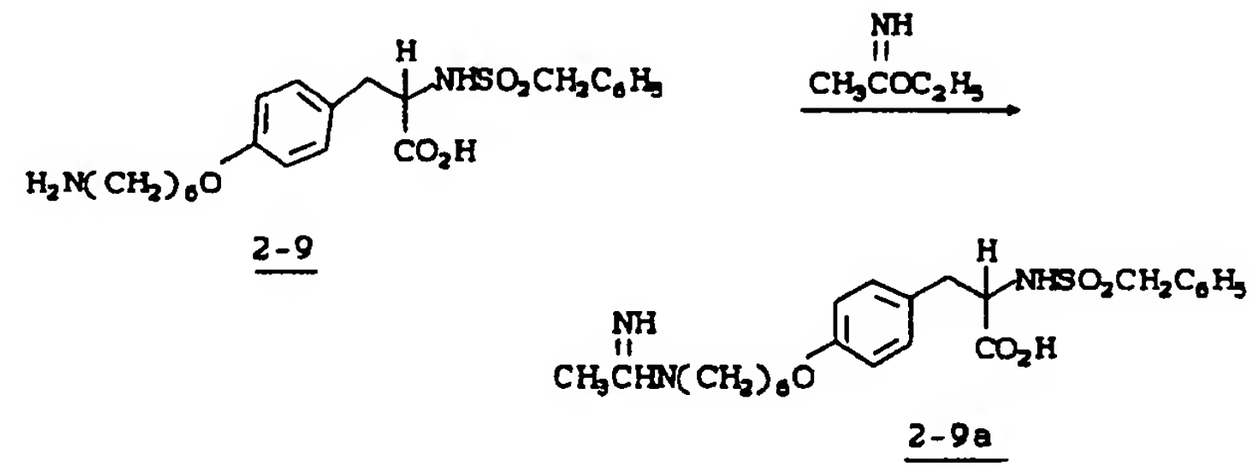


2-S-(Benzylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-9)

2-8 (0.48 g, 0.875 mmole) was treated with LiOH (0.105 g, 4.37 mmole) as described for 1-8 to give 2-S-(benzylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.4 g) as a foam.
^1H NMR (300 MHz, CD_3OD) δ 1.30-1.52 (15H, m), 1.72 (2H, m), 2.81 (1H, dd), 3.00 (3H, m), 3.93 (2H, m), 4.06 (2H, m), 6.81 (2H, d), 7.13 (2H, d), 7.20-7.32 (5H, m).

This acid (0.4g, 0.75 mmole) was dissolved in EtOAc (30 mL) and treated with HCl gas as described for 1-9. Crude reaction product was triturated with ether to give pure 2-9 (0.35 g) as a white solid.
^1H NMR (300 MHz, CD_3OD) δ 1.38-1.57 (4H, m), 1.65 (2H, m), 1.73 (2H, m), 2.71 (1H, dd), 2.89 (2H, t), 3.02 (1H, dd), 3.30 (3H, m), 3.94-4.15 (5H, m), 6.83 (2H, d), 7.15 (2H, d), 7.29 (5H, m).

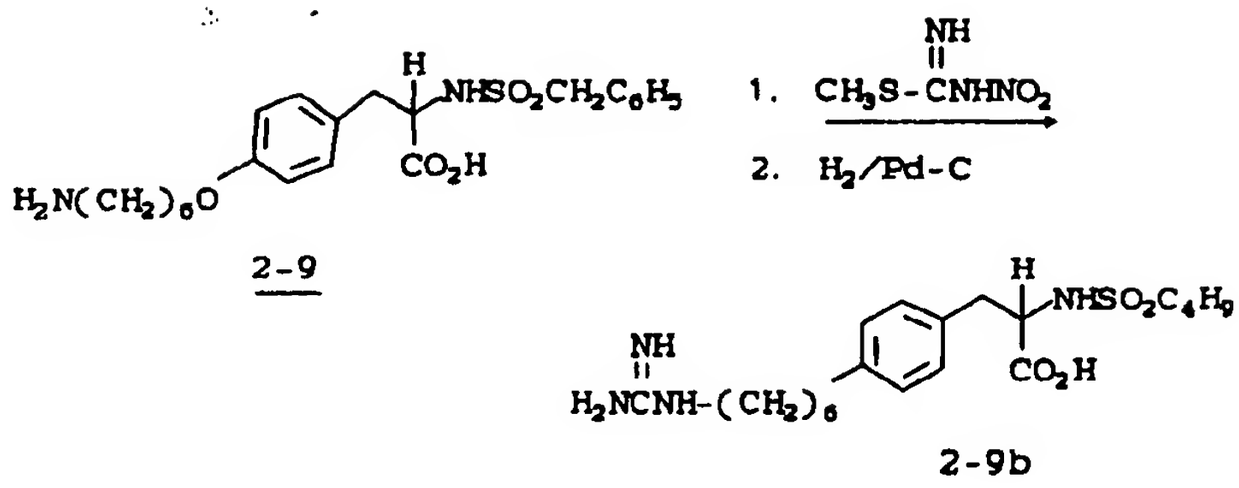
EXAMPLE 16 A



2-S-(Benzylsulfonylamino)-3-[4-(6-(acetamidinohexyloxy-phenyl)]propionic acid (2-9a)

A solution of 2-9 (1.0 g, 2.1 mmol) in THF (30 ml) is treated with ethyl acetimidate (0.18 g, 2.1 mmol) an described in Example 14A to give pure 2-9a after recrystallization from ethyl acetate.

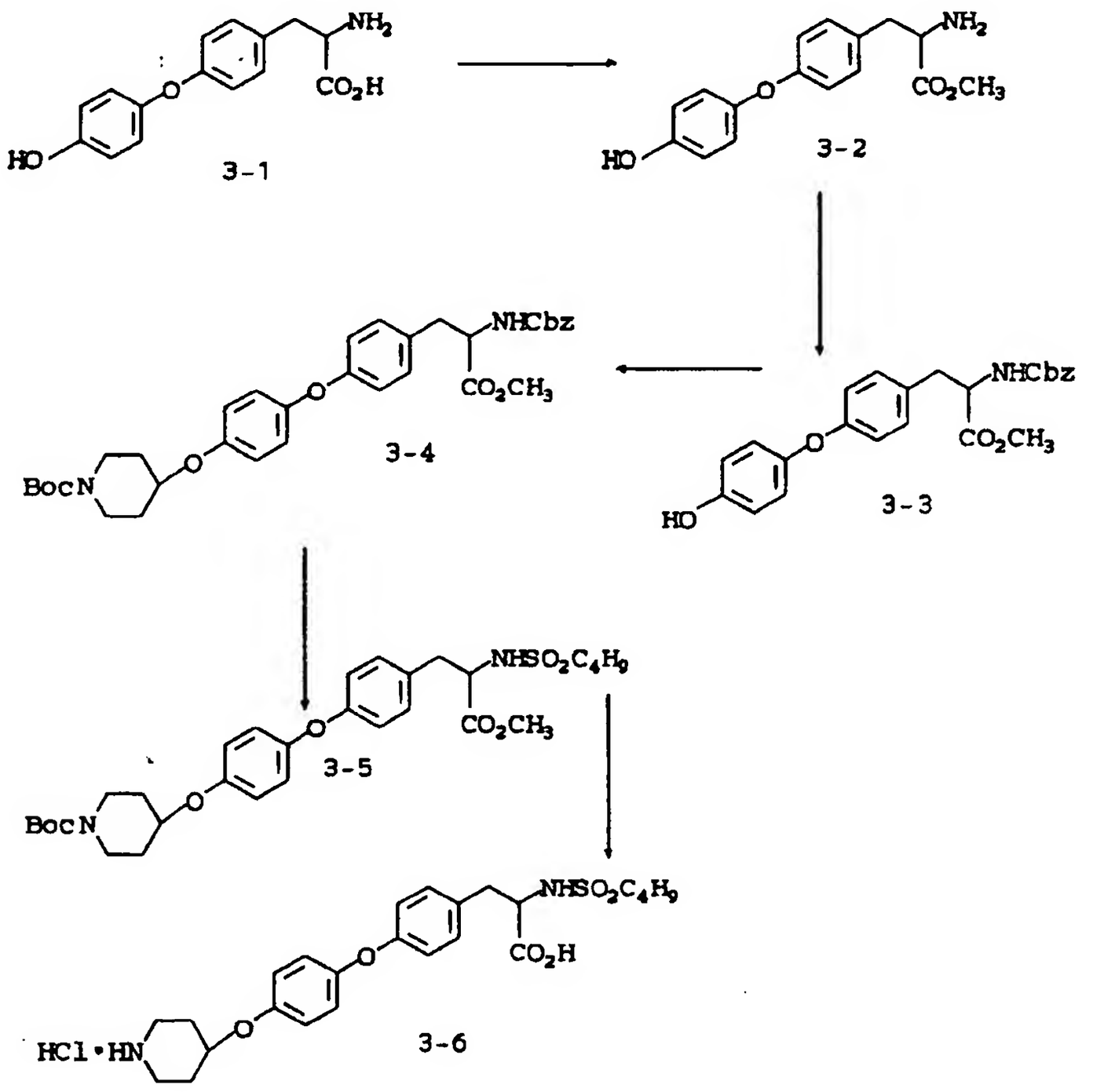
EXAMPLE 16 B



2-S-(Benzylsulfonylamino)-3-[4-(6-(guanidinohexyloxy)phenyl]propionic acid (2-9b)

A mixture of 2-9 (1.0 g, 2.1 mmol) and N-nitrosomethylthioguanidine (0.29 g, 2.1 mmol) is treated as described for Example 14C to give pure 2-9b.

SCHEME 3



Methyl 2-S-amino-3-[4-(4-hydroxyphenyl)oxyphenyl]propionate (3-2).

CH_3OH (100 ml) was cooled to 0° and treated with $SOCl_2$ (47 mmol) with stirring for 15 minutes at 0° and then 3-1 (1.5 g, 5.49 mmol) was added with stirring for 16 hours as the temperature rose to ambient.

The reaction mixture was filtered and the solvent was removed to give an oil that provided 3-2 (1.57 g) after ether washing.
^{1}H NMR (300 MHz, CD_3OD) δ 3.10-3.30 (2H, m), 3.81 (3H, s), 6.76-6.90 (6H, m), 7.20 (2H, d).

Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(4-hydroxyphenyl)oxyphenyl]propionate (3-3).

A water(1)-dioxane(1) solution (10 ml) of 3-2 (0.2 g, 0.62 mmol) was cooled to 0°C and treated with Na_2CO_3 (0.131 g, 1.23 mmole) and benzylchloroformate (0.619 mmol). After 1.5 hours of vigorous stirring, the dioxane was removed at low pressure and the residue diluted with H_2O and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and the solvent removed to provide 3-3 as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (2H, m), 3.75 (3H, s), 4.64 (1H, m), 5.10 (2H, m), 5.36 (1H, m), 6.83 (6H, m), 7.00 (2H, d), 7.37 (5H, bs).

Methyl-2-S-(N-Benzyloxycarbonylamino)-3-[4-(4-N-t-butyloxycarbonylpiperidin-4-yl)oxyphenyloxy]phenyl-propionate (3-4).

A benzene (40 ml) solution of 3-3 (0.5 g, 1.18 mmol) was treated with N-t-butyloxycarbonylpiperidin-4-ol (0.24 g, 1.18 mmol) and Ph_3P (0.310 g, 1.18 mmol) while stirring at room temperature with constant N_2 purging. Diethyl azodicarboxylate (1.18 mmol) was added and the resulting solution was stirred at room temperature for 16 hours.

The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with hexane(70)-EtOAc(30) to provide pure 3-4.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.80 (2H, m), 1.95 (2H, m), 3.08 (2H, m), 3.36 (2H, m), 3.76 (3H, s), 4.40 (1H, m), 4.63 (1H, m), 5.10 (1H, m), 5.25 (1H, m), 6.80-7.04 (8H, m), 7.36 (5H, bs).

Methyl 2-S-(Butylsulfonylamino)-3-[4-(4-N-t-butyloxycarbonylpiperidin-4-yl)oxyphenyloxy]phenylpropionate (3-5).

A solution of 3-4 (0.5 g, 0.082 mmol) in EtOH (40 ml) was treated with 10% Pd/C (125 mg) and this suspension hydrogenated in a Parr flask at 50 psi for 1.5 hour. The catalyst was filtered off and the solvent removed to give the desired amino ester as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.50-1.80 (8H, m), 1.91 (2H, m), 2.82 (1H, m), 3.04 (1H, m), 3.34 (2H, m), 3.76 (3H, s), 4.20 (1H, m), 7.90 (8H, m), 8.11 (2H, d).

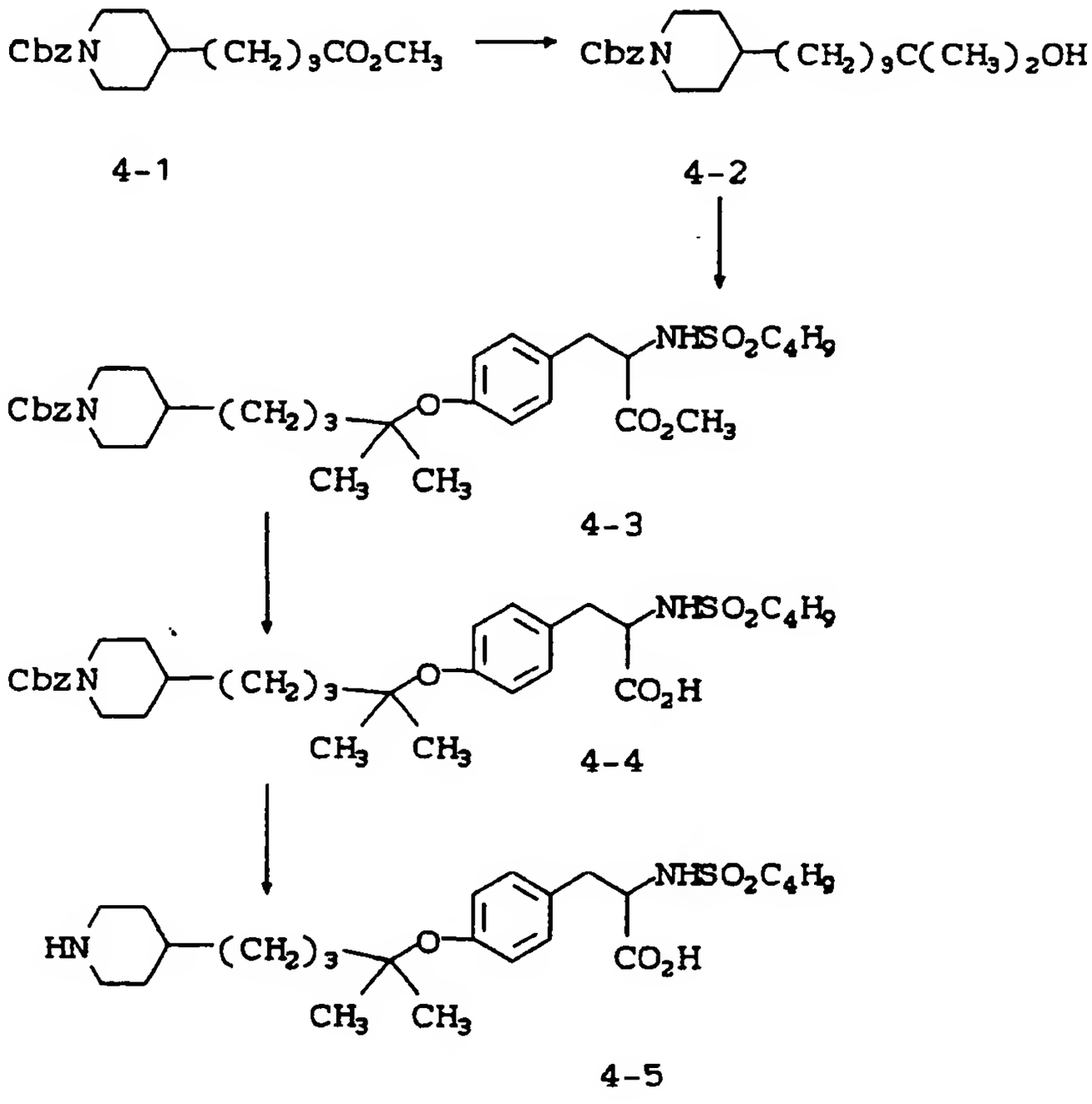
This amino ester (0.36 g, 0.77 mmol) was dissolved in EtOAc (10 ml) and treated with $NaHCO_3$ (0.386 g, 4.6 mmol) and n-butylsulfonylchloride (1.53 mmol) with heating at reflux for 48 hours. The solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane(65)-EtOAc(35) to provide pure 3-5 as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88-1.02 (4H, m), 1.25-1.45 (3H, m), 1.50 (9H, s), 1.51-1.80 (2H, m), 1.93 (2H, m), 2.80 (2H, m), 2.95-3.20 (2H, m), 3.21-3.40 (2H, m), 3.72 (2H, m), 3.74 (3H, s), 4.38 (2H, m), 4,80 (1H, d), 6.90 (6H, m), 7.10-7.27 (2H, m).

2-S-(Butylsulfonylamino)-3-[4-(piperidin-4-yl)oxyphenyloxy]phenylpropionic acid hydrochloride (3-6).

A solution of 3-5 (0.2 g, 0.34 mmol) in THF(1)-H_2O(1)-CH_3OH(1) was treated with LiOH (0.075 g, 1.78 mmol) at room temperature for 8 hours. The solvent was removed and the residue was acidfied with 10% $KHSO_4$ solution and this extracted several times with EtOAc. The organic extracts were combined, washed with brine, dried ($NaSO_4$) and the solvent removed to give the desired acid. R_f = 0.3 [silica gel, 97($CHCl_3$)-3(CH_3OH)-1(HOAc)].
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t), 1.20-1.30 (3H, m), 1.46 (9H, s), 1.50-2.0 (6H, m), 2.75 (2H, m), 2.97 (1H, m), 3.18 (1H, m), 3.33 (2H, m), 3.76 (2H, m), 4.35 (2H, m), 5.07 (1H, m), 6.89 (6H, m), 7.13 (2H, m).

This acid (0.15 g, 0.26 mmol) was dissolved in EtOAc and treated with HCl gas as described for 1-9 to give pure 3-6 as a white solid.
^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (3H, t), 1.32 (2H, m), 1.53 (2H, m), 1.97-2.21 (4H, m), 2.75 (2H, m), 2.63 (1H, m), 3.20 (3H, m), 3.40 (2H, m), 4.14 (1H, m), 6.82-7.05 (6H, m), 7.23 (2H, m).

SCHEME 4



4[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2-methyl]pentan-2-ol(4-2).

Methyl 4-(N-Benzyloxycarbonylpiperidin-4-yl)butanoate (4-1) (10.07 g, 0.032 mol) in THF (200 ml) was cooled to 0°C and treated with CH_3MgI (0.095 mol) for 3.0 hours. The reaction mixture was poured into ice, acidified with 10% $KHSO_4$ and extracted with 3 portions of EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$) and the solvent removed. The residue was purified by flash chromatography on silica gel eluting with hexane(7)-EtOAc(3) to give pure 4-2. R_f = 0.3 (silica gel, hexane (7)-EtOAc(3).

Methyl 2-S-(Butylsulfonylamino)-3-[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2,2-dimethyl]butyloxyphenyl-propionate (4-3).

N-n-Butylsulfonyl-L-tyrosine methyl ester (7.21 g, 0.023 mole) was dissolved in a mixture of 4-2(1.0g), CH_2Cl_2 (30 ml) and benzene (250 ml). Triphenylphosphine (5.97 g, 0.023 mole) was added and after purging with N_2, diethyl azodicarboxylate (3.6 ml, 0.023 mole) was added at room temperature as the reaction mixture turned red-orange in color. Reaction mixture stirred at room temperature for 7 days. Solvent was removed and the residue was purified by flash chromatography on silica gel eluting with hexane(60)-EtOAc(40) to give pure 4-3.

^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (6H, t), 1.10-1.40 (12H, m), 1.43-1.78 (8H, m), 2.70-2.82 (4H, m), 2.95-3.10 (3H, m), 3.75 (3H, s), 4.18 (2H, m), 4.32 (1H, m), 5.13 (2H, s), 6.88 (2H, d), 7.06 (2H, d), 7.38 (5H, m).

2-S-(Butylsulfonylamino)-3-[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2,2-dimethyl]butyloxyphenylpropionic acid (4-4).

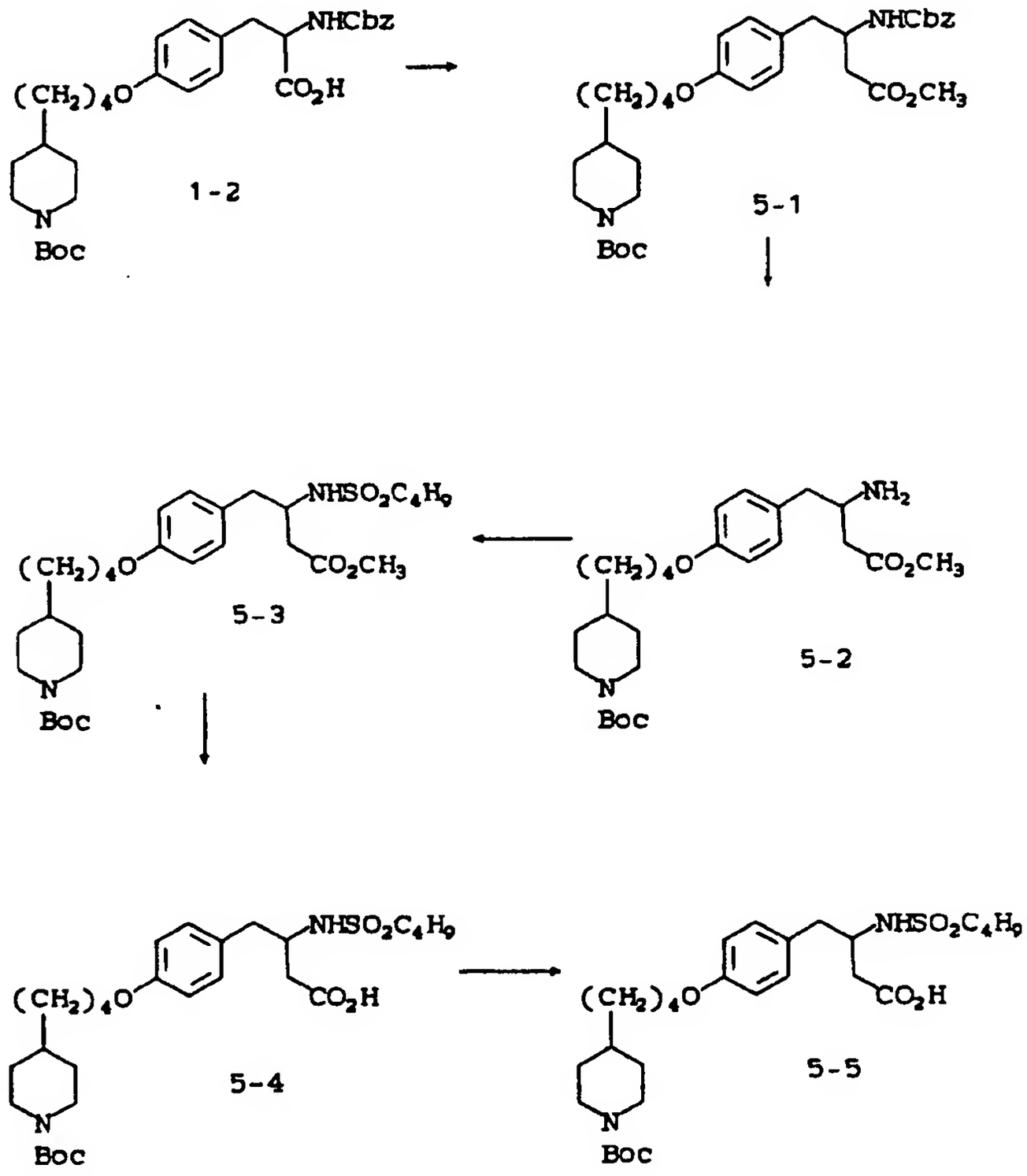
Dissolved 4-3 (0.64 g, 0.001 mole) in THF/H_2O/CH_3OH mixture and treated with LiOH (0.26 g, 0.0062 mole) at room temperature for 8 hours. Solvent removal, acidification ($KHSO_4$ solution) and EtOAc extraction provided

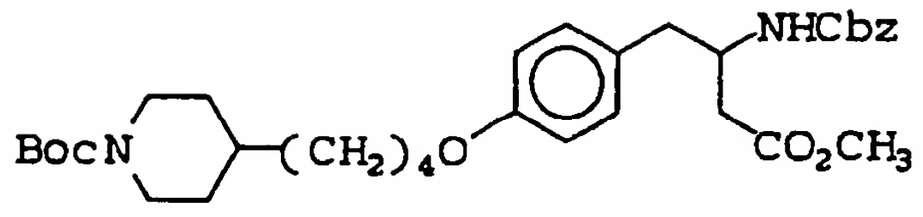
crude 4-4 which was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-CH_3OH(3)-HOAc(1) to give pure 4-4.
^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (6H, s), 1.05-1.50 (13H, m), 1.55-1.80 (5H, m), 2.77 (4H, m), 3.04 (2H, m), 4.10 (2H, bd), 4.17 (1H, m), 4.85 (1H, d), 5.14 (2H, s), 6.88 (2H, d), 7.13 (2H, d), 7.39 (5H, m).

2-S-(Butylsulfonylamino)-3-[4-(piperidin-4-yl)-2,2-dimethyl]butyloxyphenylpropionic acid (4-5).

To ammonium formate (0.23 g, 3.65 mmol) in CH_3OH (5 ml) was added 4-4 (0.22 g, 3.65 mmole) in 10 ml CH_3OH and then 10% Pd/C (100 mg) was added at room temperature. After 15 minutes the reaction mixture was passed thru a Solka Floc pad and the solvent removed. This residue was purified by flash chromatography on silica gel eluting with EtOH(9)-H_2O(1)-NH_4OH(1) to give pure 4-5.
^1H NMR (300 MHz, CD_3OD) δ 0.88 (6H, s), 1.15-1.40 (12H, m), 1.42-1.70 (7H, m) 1.90 (2H, d), 2.78-3.00 (6H, m), 3.06 (1H, dd), 3.35 (3H, m), 3.93 (1H, m), 6.86 (2H, d), 7.20 (2H, d).

SCHEME 5

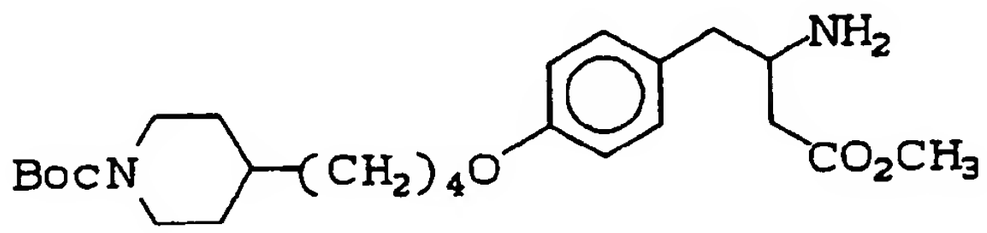




5-1

Methyl 3-S-(Benzyloxycarbonylamino)-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-1).

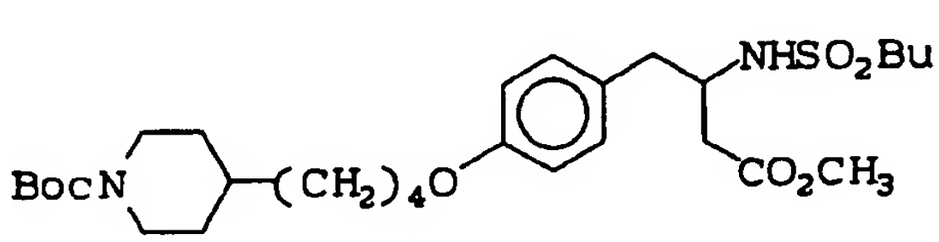
A solution of compound 1-2 (1.0 g, 1.8 mmole) and N-methylmorpholine (0.21 mL, 1.9 mmole) in EtOAc (10 mL) was stirred at -15°C and treated with isobutyl chloroformate (0.24 mL, 1.8 mmole). After 15 minutes the heterogeneous mixture was treated portion-wise with an ethereal solution of diazomethane (0.5M:10 mL, 5.0 mmole), followed by continued stirring at 0° for 1.0 hour. The reaction mixture was then purged with argon for 10 minutes to remove excess diazomethane. The organic phase was washed with 2 x 5 mL portions of H_2O, brine, dried ($MgSO_4$), and evaporated. The residue was then dissolved in CH_3OH (15 mL) and treated sequentially with triethylamine (0.7 mL, 5.0 mmole) and AgO_2CPh (110 mg, 0.5 mmole) while stirring at ambient temperature to effect vigorous gas evolution. After 30 minutes the solvent was evaporated and then the crude reaction product purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give 5-1 (0.52 g) as an oil.
TLC R_f = 0.23 (30% EtOAc/hexane)



5-2

Methyl 3-S-Amino-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-2).

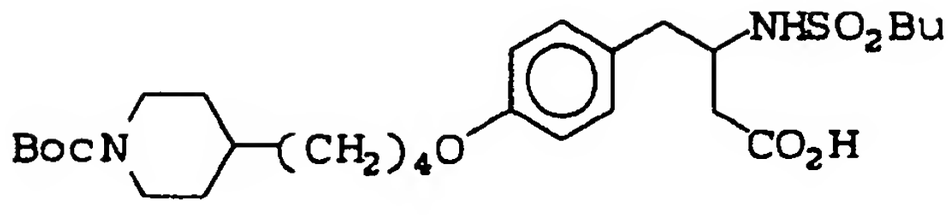
To 5-1 (0.52 g, 0.9 mmole) dissolved in absolute ethanol (20 mL) was added 10% Pd/C (0.25 g) and the resulting suspension was hydrogenated under balloon pressure for 12 hours. The catalyst was then filtered off and the solvent was removed in vacuo to give 5-2 (0.35 g) as an oil.
TLC R_f = 0.15 (9:1:1 $CH_2Cl_2/CH_3OH/AcOH$).



5-3

Methyl 3-S-(Butylsulfonylamino)-4-[4-N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-3).

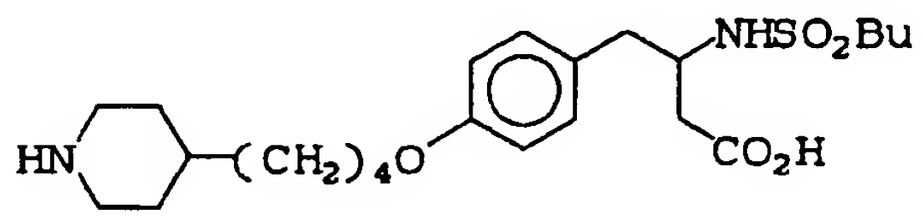
To 5-2 (0.36 g, 0.8 mmole), triethylamine (170 µL, 1.2 mmole), 4-dimethylaminopyridine (12 mg, 0.1 mmole), and THF (5 mL) at 0°C was added n-butylsulfonyl chloride (130 µL, 1.0 mmole) with stirring. The cooling bath was removed and stirring was continued for 6 hours. The reaction mixture was diluted with 10 mL of EtOAc and then washed with 2x5 mL H_2O, brine, dried ($MgSO_4$), and concentrated. The crude reaction product was purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give 5-3 (180 mg) as an oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.25-1.83 (13H, m), 1.29 (3H, t), 1.47 (9H, s), 2.68 (6H, m), 2.87 (2H, d), 3.73 (3H, s), 3.93 (2H, t), 4.08 (1H, m), 4.72 (1H, d), 6.87 (2H, d), 7.12 (2H, d).



5-4

3-S-(Butylsulfonylamino)-4-[4-N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butanoic acid (5-4).

Compound 5-3 (175 mg, 0.33 mmole) in CH_3OH (4.0 mL) was treated with IN NaOH (1.0 mL, 1.0 mmole) followed by continued stirring at ambient temperature for 20 hours. The reaction mixture was diluted with 15 mL EtOAc and then washed with 10 mL 5% $KHSO_4$ and brine, dried ($MgSO_4$), and concentrated to give 5-4 (160 mg) as an oil.
TLC R_f = 0.31 (9:0.5:0.5 $CH_2Cl_2/CH_3OH/AcOH$).

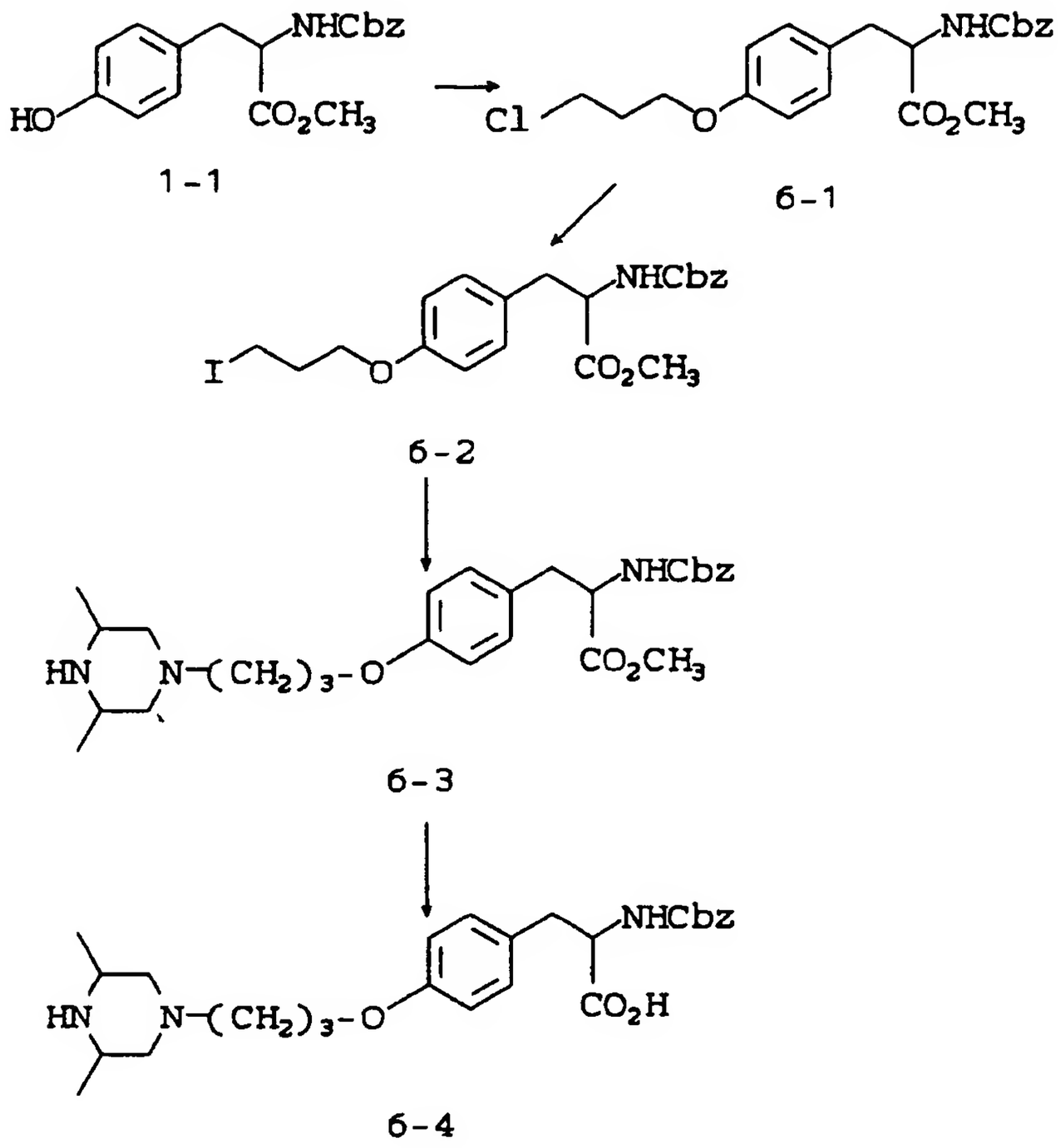


5-5

3-S-(Butylsulfonylamino)-4-[4-piperidin-4-yl)butyloxyphenyl]butanoic acid (5-5)

To a stirred solution, of compound 5-4 (160 mg, 0.30 mmole), CH_2Cl_2 (2.0 mL), and anisole (100 μL) at 0°C was added CF_3CO_2H (1.0 mL). After 1.5 hours at 0°C the solvents were evaporated and the crude reaction product purified by flash chromatography on silica gel eluting with 10:0.8:0.8 ethanol/H_2O/conc. NH_4OH to give 5-5 (42 mg) as a solid.
^1H NMR (300 MHz, D_2O/CF_3CO_2D) δ 0.82 (3H, t), 1.10-1.70 (11H, m), 1.80 (m, 2H), 1.98 (m, 2H), 2.48 (2H, t), 2.72 (3H, m), 3.00 (3H, m), 3.43 (2H, m), 3.96 (1H, m), 4.10 (2H, t), 7.01 (2H, d), 7.32 (2H, d).

SCHEME 6



Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(3-chloropropyloxyphenyl)propionate (6-1).

Treatment of a DMF solution of 1-1 (0.95 g, 2.9 mmol) and 3-chloro-1-tosyloxypropane (0.84 g, 3.19 mmol) with cesium carbonate (0.47 g, 1.45 mmole) gave a solution that was stirred at room temperature overnight. The reaction mixture was then diluted with H_2O and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and the solvent removed to give an oily residue. This was purified by flash chromatography on silica gel eluting with EtOAc(5)-hexane(95) to afford 6-1 as a clear oil. R_f 0.5 (silica gel eluting with EtOAc(30)-hexane(70).

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(3-iodopropyloxyphenyl)propionate (6-2).

A solution of 6-1 (0.6 g, 1.5 mmol) in acetone was treated with sodium iodide (1.1 g, 7.5 mmol) and the resulting solution was heated at reflux for 16 hours. The reaction mixture was then diluted with ether, washed with water, brine and dried (Na_2SO_4). Solvent removal gave an oil that was purified by flash chromatography on silica gel eluting with hexane(90)-EtOAc(10) to give 6-2 as a clear oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.85-2.08 (4H, m), 3.04 (2H, m), 3.26 (2H, t), 3.71 (3H, s), 3.95 (2H, t), 4.60 (1H, m), 5.00-5.21 (3H, m), 6.78 (2H, d), 6.99 (2H, d), 7.33 (5H, m).

Methyl 2-S-(N-Benyzloxycarbonylamino)-3-[4-(2,6-dimethylpiperazin-4-yl)propyloxyphenyl]propionate (6-3).

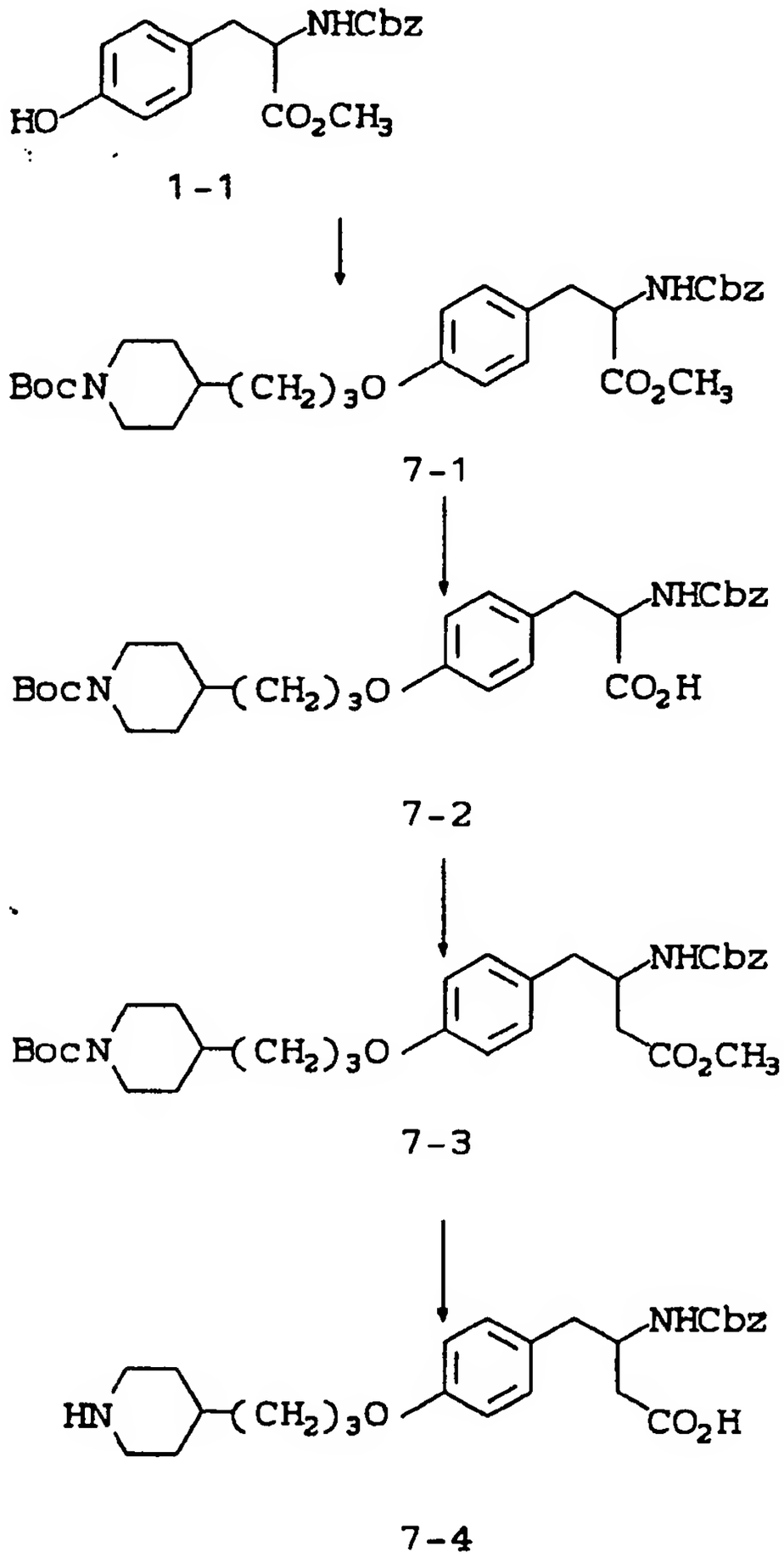
A solution of 6-2 (0.1 g, 0.2 mmol) and 2,6-dimethylpiperazine (0.068 g, 0.6 mmol) in 1 ml THF was stirred at room temperature for 20 hours. The solvents were removed at low pressure to provide 6-3 as a clear oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (4H, d), 1.82 (3H, m), 2.65 (2H, m), 2.79 (2H, m), 3.05 (1H, m), 3.18 (2H, bd), 3.60 (1H, m), 3.72 (3H, s), 3.96 (2H, m), 4.62 (1H, m), 5.10 (2H, s), 5.21 (1H, m), 6.79 (2H, d), 7.00 (2H,

d), 7.35 (5H, bs).

2-(N-Benzyloxycarbonylamino)-3-[4-(2,6-dimethylpiperazin-4-yl)propyloxyphenyl]propionic acid (6-4).

6-3 (0.090 g, 0.2 mmol) in methanol was treated with IN NaOH (0.7 ml) at room temperature for 16 hours. The solvent was removed to give crude acid which was purified by flash chromatography on silica gel eluting with isopropanol(10)-NH_4OH(l)-H_2O(l) to provide pure 6-4, R_f 0.25.
^1H NMR (300 MHz, CD_3OD) δ 1.65-1.85 (4H, m), 2.60-2.70 (2H, m), 2.80-2.95 (6H, m), 3.11 (8H, m), 3.52 (2H, m), 3.65-3.75 (2H, m), 3.82 (2H, t), 4.17 (1H, m), 4.70 (2H, s), 4.85 (2H, m), 6.63 (2H, d), 6.92 (2H, d), 7.10 (5H, bs).

SCHEME 7



Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl]propionate (7-1).

A solution of 1-1 (4.0 g, 2.6 mmol) and 3-(N-Boc-piperidin-4-yl)propyl iodide (1.1 g, 3.3 mmol) in 40 ml DMF was treated with cesium carbonate (0.4 g, 1.35 mmol) and the resulting solution was stirred at room temperature for 20 hours. The solvent was removed and the residue was taken up in EtOAc, washed with water, brine and dried (Na_2SO_4). Solvent removal provided a residue that was purified by flash chromatography on silica gel eluting with 4:1 hexane(80)-EtOAc(20) to give pure 7-1 as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.37-1.45 (11H, m), 1.65-1.82 (4H, m), 2.68 (2H, m), 3.03 (2H, m), 3.71 (3H, s), 3.90 (2H, t), 4.08 (2H, bd), 4.61 (1H, m), 5.10 (1H, s), 5.18 (1H, m), 6.79 (2H, d), 7.00 (2H, d), 7.35 (5H, bs).

2-(S)-(N-Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl]propionic acid (7-2).

7-1 (0.5 g, 0.9 mmol) in methanol (12 ml) was treated with IN NaOH (3 ml) at room temperature for 16 hours. The solvent was then removed and the residue acidified with 5% $KHSO_4$ solution. This was extracted with EtOAc several times and the combined organic extracts were washed with brine and dried (Na_2SO_4). Solvent removal gave 7-2 as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.37-1.52 (12H, m), 1.62-1.85 (5H, m), 2.66 (2H, t), 3.10 (2H, m), 4.89 (2H, t), 4.10 (4H, m), 4.62 (1H, m), 5.09 (1H, s), 5.19 (1H, m), 6.79 (2H, d) 7.03 (2H, d), 7.34 (5H, bs).

Methyl 3-S-(N-Benzyoxycarbonylamino)-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl)butanoate (7-3).

To a stirred solution of 7-2 (1.6 g, 2.9 mmol) in EtOAc at -15°C was added isobutylchloroformate (2.9 mmol) and N-methylmorpholine (2.9 mmol) and the resulting solution was stirred for 0.5 hours at -15°. Then, diazomethane (5.0 mmol in Et_2O) was added and the reaction mixture was stirred at 0° for 20 minutes. The reaction mixture was purged with argon, diluted with EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and the solvent removed to provide the desired diazoketone.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.35-1.50 (12H, m), 1.55-1.85 (6H, m), 2.68 (2H, bt), 2.95 (2H, d), 3.90 (2H, t), 4.09 (3H, m), 4.42 (1H, m), 5.06 (1H, m), 5.20 (1H, m), 5.35 (1H, m), 6.80 (2H, d), 7.06 (2H, d), 7.35 (5H, bs).

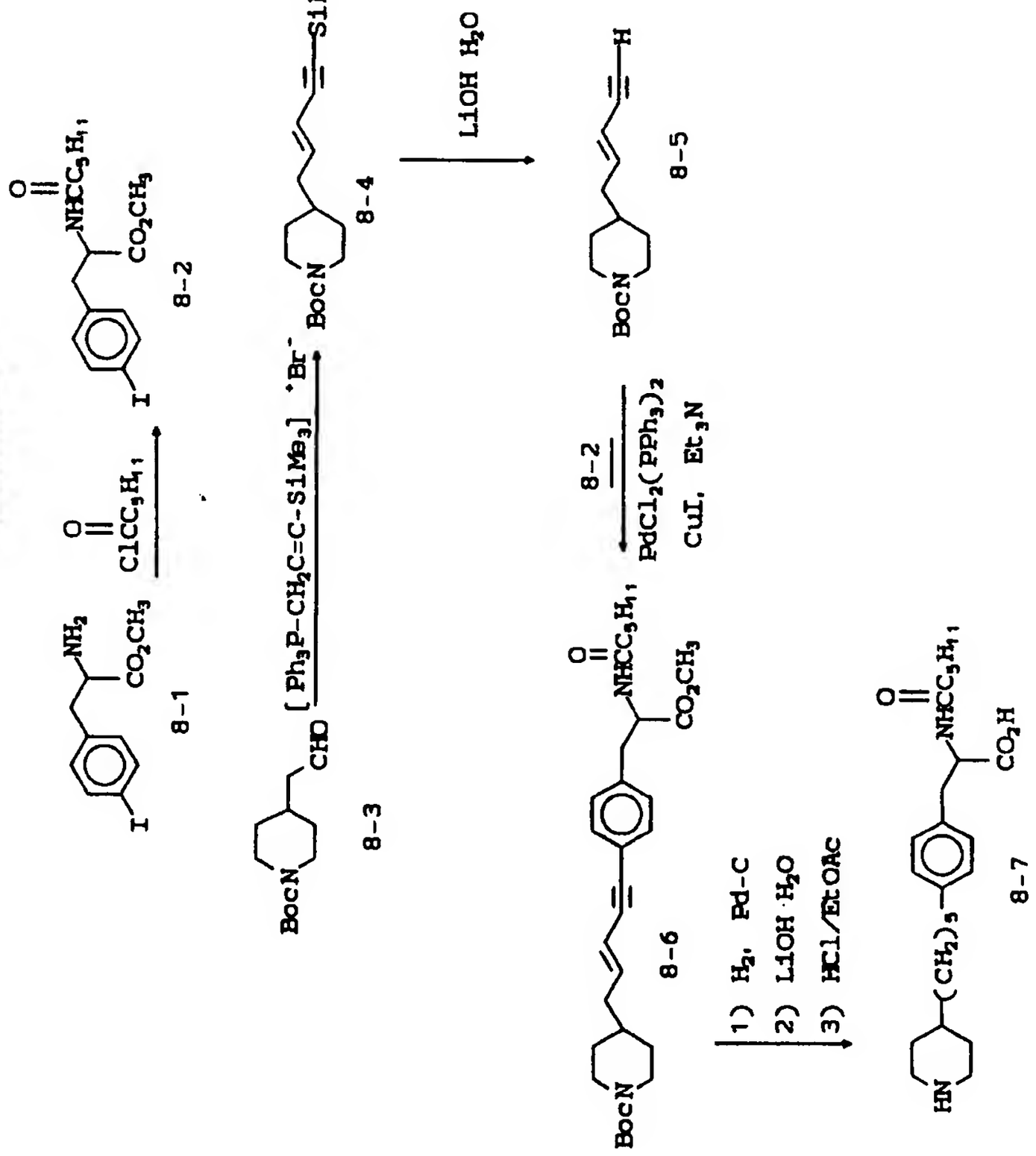
This diazoketone (1.63 g, 2.9 mmol) was dissolved in CH_3OH (20 ml) and treated at room temperature with a CH_3OH solution (5 ml) of silver benzoate (0.22 mg, 0.96 mmoles) and triethylamine (1.25 ml). After a few minutes the reaction became black with gas evolution apparent. After 0.5 hours the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with 4:1 hexane(80) EtOAc(20) to give 7-3 as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.37-1.47 (12H, m), 1.60 (2H, s), 1.65-1.83 (4H, m), 2.49 (2H, m), 2.62-2.91 (4H, m), 3.67 (3H, s), 3.90 (2H, t), 4.03-4.20 (4H, m), 5.08 (2H, s), 5.24 (1H, m), 6.79 (2H, d), 7.05 (2H, d), 7.32 (5H, bs).

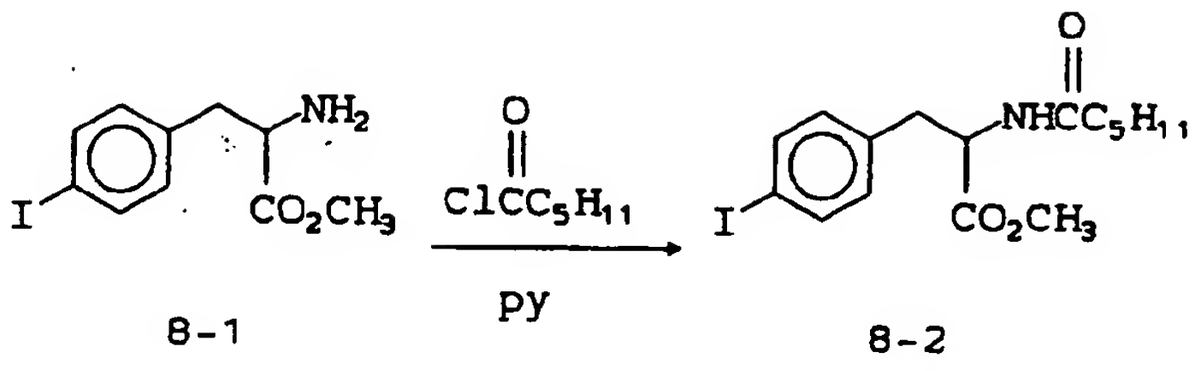
3-S-(N-Benzyloxycarbonylamino)-4-[4-(piperidin-4-yl)propyloxyphenyl]butanoic acid (7-4).

A solution of 7-3 (0.3 g, 0.53 mol) was treated with IN NaOH (1.7 ml) and the resulting mixture was stirred at room temperature for 16 hours. The solvent was removed and the residue acidified with 5% aq $KHSO_4$ solvent and this was extracted several times with EtOAc. The combined organics were washed with brine, dried ($NaSO_4$) and the solvent removed to give the desired acid.
^{1}H NMR (300 MHz, CD_3OD) δ 1.10 (2H, m), 1.40-1.52 (12, m), 1.65-1.84 (6H, m), 2.54-2.93 (8H, m), 3.92 (2H, t), 4.05-4.12 (3H, m), 5.10 (2H, s), 6.71 (2H, d), 7.08 (2H, d), 7.35 (5H, m).

This acid was dissolved in CH_2Cl_2 (4 ml) and anisole (0.41 mmole) was added, followed at 0° with trifluoroacetic acid (2 ml). After 2.5 hours stirring at 0°, the solvents were removed and the residue purified by flash chromatography on silica gel eluting with EtOH(10)-NH_4OH(l)-H_2O(l) to give pure 7-4 as a white solid.
^{1}H NMR (300 MHz, CD_3OD) δ 1.3-1.5 (4H, m), 1.6 (1H, m), 1.75-1.85 (2H, m), 1.95 (2H, d), 2.54 (2H, m), 2.72 (2H, m), 2.93 (2H, t), 3.32 (6H, m), 3.92 (2H, t), 4.11 (1H, m), 4.95 (2H, m), 6.75 (2H, d), 7.05 (2H, d), 7.25 (5H, m).

SCHEME 8


8-1
8-2
8-3
8-4
8-5
8-6
8-7
BocN
HN
LiOH H2O
PdCl2(PPh3)2
CuI, Et3N
1) H2, Pd-C
2) LiOH·H2O
3) HCl/EtOAc

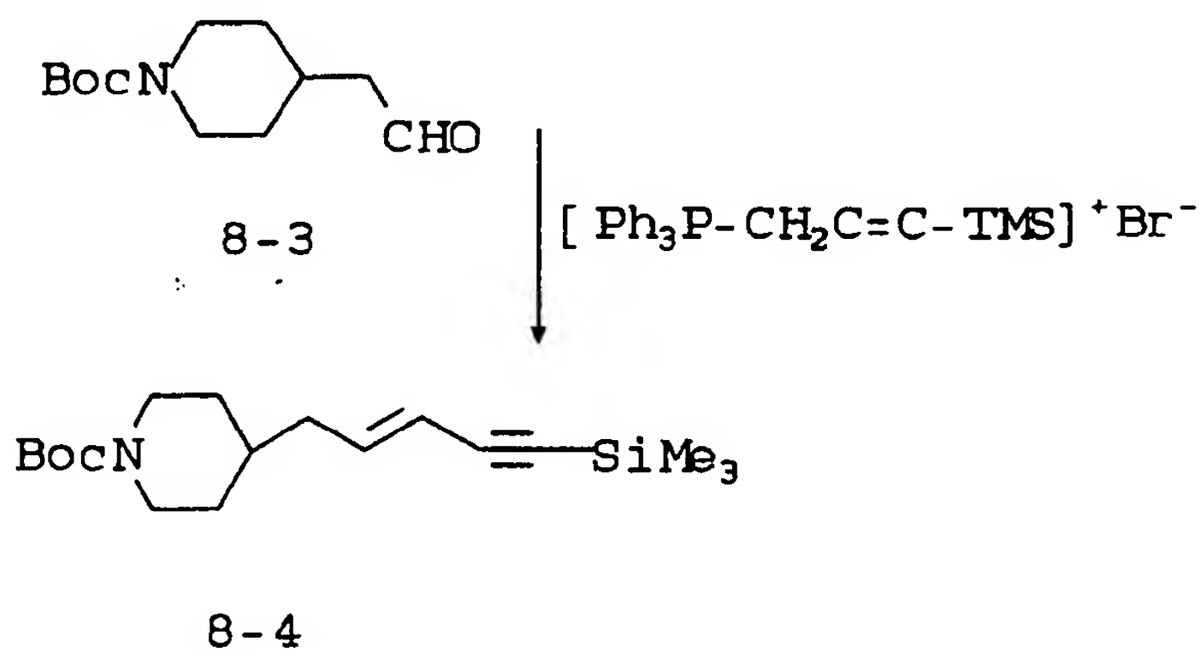


8-1 8-2

Methyl 2-S-(Hexanoylamino)-3-(4-iodophenyl)propionate (8-2)

A suspension of 8-1 (1.01 g, 2.96 mmoles) in 20 ml $CHCl_2$ was cooled to 0° and pyridine (1.43 ml, 17.7 mmoles) was added followed by hexanoylchloride (1.25 ml, 8.88 mmoles). After 20 minutes all 8-1 was consumed. Water (25 ml) was then added carefully and this mixture was extracted with EtOAc (150 ml). The separated organic phase was washed with 10% $KHSO_4$, brine, dried (Na_2SO_4) and the solvent was removed to give a white solid. This was purified by flash chromatography on silica gel eluting with 5% $Et_2O/CHCl_3$ to give pure 8-2 (1.07 g) as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t), 1.27 (4H, m), 1.60 (2H, m), 2.09 (2H, t), 3.05 (2H, m), 3.75 (3H, s), 4.88 (1H, m), 5.93 (1H, m), 6.83 (2H, d), 7.60 (2H, d).

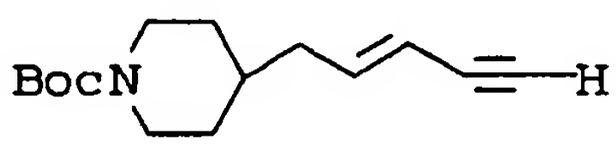


8-3 8-4

5-(N-t-Butyloxycarbonylpiperidin-4-yl)-1-trimethyl-1-silylpent-3-ene-1-yne (8-4).

A suspension of 3-trimethylsilyl-2-propynyl)triphenyl phosphonium bromide (3.0 g, 6.62 mmoles) (Aldrich) in 50 ml THF was cooled to -78° and treated with n-BuLi (6.62 mmoles) dropwise. The resulting solution was allowed to warm to -40° and was then stirred for 0.5 hours to give a deep red solution. After cooling to -78°C the reaction mixture was treated with 8-3 (1.07 g, 4,73 mmoles) in 15 ml THF and was allowed to warm to 0° with stirring for 1 hour. The reaction was quenched with 50 ml H_2O and this was extracted with EtOAc (200 ml). The organic phase was separated, dried (Na_2SO_4) and stripped to provide as residue that was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexane to provide pure 8-4, (2.02 g), R_f = 0.3.

^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 0.70-1.10 (4H, m), 1.10-1.40 (13H, m), 1.40-1.60 (3H, m), 1.83 38H, m), 2.40-2.60 (3H, m), 3.85 (3H, m), 5.35 (1H, t), 6.00 (1H, m).

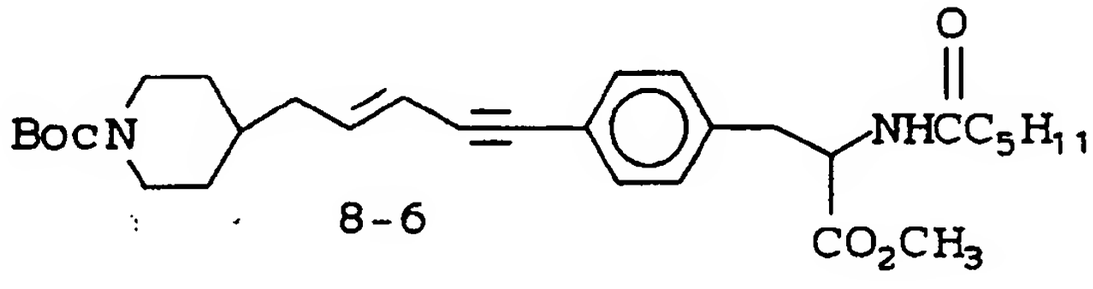


5-(N-t-Butyloxycarbonylpiperidin-4-yl)pent-3-en-1-yne (8-5)

A solution of 8-4 (0.815 g, 2.54 mmoles) in 60 ml THF was treated with 12 ml H_2O and lithium hydroxide hydrate (0.96 g, 2.28 mmoles). The reaction mixture was stirred at room temperature for 6 hours during which time the color became dark orange. The reaction mixture was then diluted with Et_2O (75 ml) and the aqueous

phase was separated and washed with 3x75 ml Et_2O. The combined organic extacts were washed with brine, dried and stripped. The resulting residue was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to give 0.63 g pure 8-5.

^1H NMR (300 MHz, $CDCl_3$) δ 1.0-1.25 (3H, m), 1.25-1.60 (11H, m), 1.60-1.75 (3H, m), 2.06 (2H, t), 2.30 (1H, t), 2.60-2.78 (2H, m), 4.07 (2H, m), 5.51 (1H, m), 6.22 (1H, m).



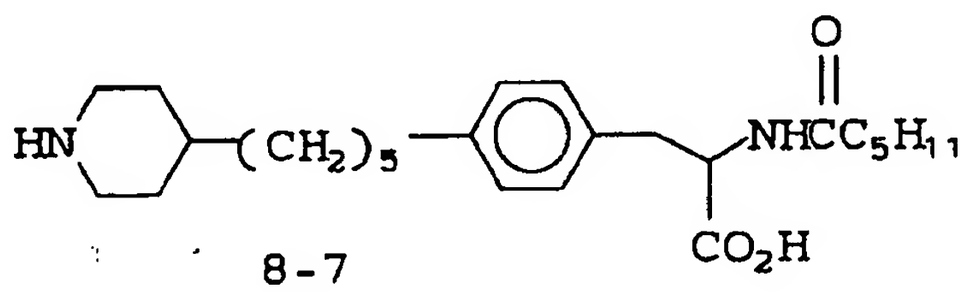
8-6

Methyl 2-S-(Hexanoylamino)-3-[4-(5-N-t-butyloxycarbonylpiperidin-4-yl)pent-3-ene-1-ynephenyl]propionate (8-6).

A solution of 8-5 (0. 3 g, 1.2 mmoles) and 8-2 (0.58 g, 1.4 mmoles) in diethylamine (6 ml) was purged with N_2 and bis-triphenylphosphine palladium chloride (0.049 g, 0.07 mmoles) was added followed by cuprous iodide (7 mg, 0.035 mmoles) and the suspension was purged again. After several minutes the reaction mixture became homogeneous and this solution was stirred for 16 hours at room temperature.

The solvent was removed at high vacuum and the residue was dissolved in pH 7 buffer and extracted with Et_2O. The organic extract was washed with 10% $KHSO_4$, brine, then dried (Na_2SO_4) and stripped. The residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/hexanes to give 0.28 g pure 8-6. R_f = 0.3 (20% EtOAc, hexanes).

^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, m), 1.05-1.40 (9H, m), 1.52 (6H, s), 1.58-1.75 (4H, m), 2.07 (2H, m), 1.70 (2H, m), 3.14 (2H, m), 3.75 (2H, m), 4.10 (2H, m), 4.89 (1H, m), 5.70 (1H, m), 5.94 (1H, m), 6.18 (1H, m), 7.03 (2H, m), 7.38 (2H, m).



8-7

2-S-(Hexanoylamino)-3-[4-(5-Piperidin-4-yl)pentylphenyl]propionic acid (8-7)

8-6 (0.275 g, 0.52 mmoles) was dissolved in EtOH and 2 ml of H_2O was added along with 5 drops of HOAc. Pd-C (100 mg) was added and the resulting suspension was hydrogenated on a Paar shaker (50 psi) for 4 hours. The reaction mixture was filtered through Solka-Floc and the resulting solvent was removed. The resulting residue was purified by flash chromatography on silica gel eluting with 35% EtOAc/hexanes to give 0.22 g of methyl 2-S-hexanoyl amino-3-[4-5-N-t-butyloxycarbonylpiperidin-4-yl)pentylphenyl propionate.

^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t), 1.00-1.35 (12H, m), 1.45 (9H, s), 1.50-1.65 (6H, m), 2.15 (2H, t), 2.50-2.65 (4H, m), 3.05 (2H, m), 3.71 (3H, s), 4.04 (2H, m), 4.83 (1H, m), 5.96 (1H, m), 6.98 (2H, d), 7.04 (2H, d).

This ester (0.17 g, 0.32 mmoles) was suspended in 10 ml of 1:1 THF/H_2O and CH_3OH (2 ml), lithium hydroxide hydrate (0.067 g, 1.6 mmoles) was added and the reaction was stirred for 2.0 hours at room temperature. The solvent was then removed and the residue was taken up in H_2O. This was acidified to pH 2-3 with 10% $KHSO_4$, and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and stripped to give 0.050g of the desired acid.

^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, m), 0.95-1.42 (15 H, m), 1.47 (9H, s), 1.50-1.70 (7H, m), 2.18 (2H, m), 2.48-2.72 (5H, m), 5.02-5.30 (2H, m), 4.03 (2H, m), 4.84 (1H, m), 6.05 (1H, m), 7.06 (4H, s).

This acid (0.15 g, 0.29 mmoles) was dissolved in EtOAc (25 ml), cooled to -70° and treated with HCl gas for 10 minutes. The temperature was allowed to rise to -20° over 0.5 hr. The reaction mixture was purged with N_2 and the solvent was removed. The residue purified by flash chromatography on silica gel eluting with 9:1:1 EtOH/H_2O/NH_4OH to give pure 8-7, 0.040 g as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 0.78 (3H, t), 1.05-1.30 (9H, m), 1.32-1.56 (4H, m), 1.74 (2H, d), 2.03 (2H, m),

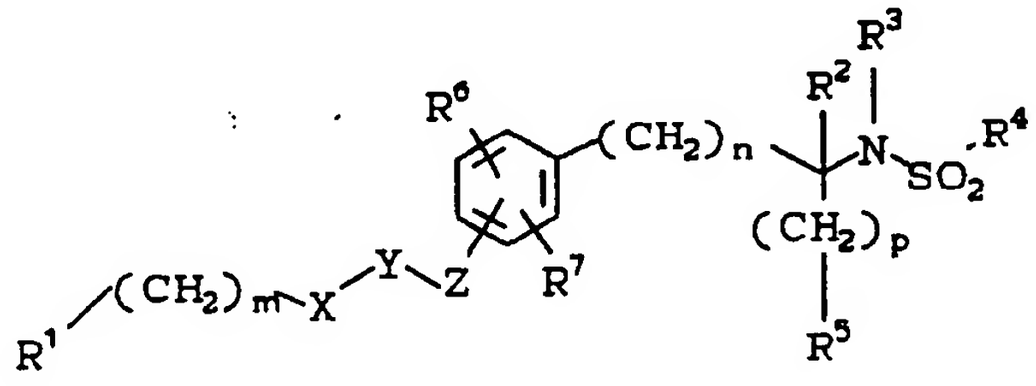
2.42 (2H, m), 2.70-2.85 (3H, m), 3.04 (1H, dd), 3.21 (2H, m), 4.38 (1H, m), 6.92 (2H, d), 7.00 (2H, d).

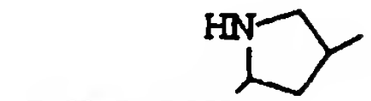
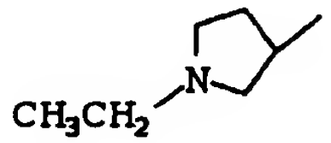
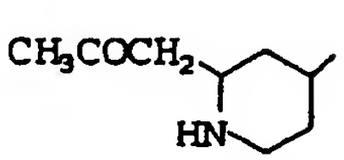
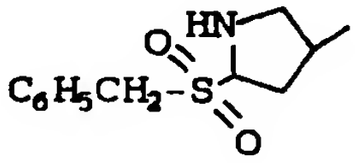
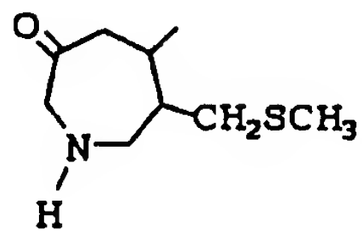
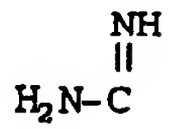
In the above Schemes and Examples, various reagent symbols have the following meanings:

BOC: t-butoxycarbonyl.
Pd-C: Palladium on activated carbon catalyst.
DMF: Dimethylformamide.
CBZ: Benzyloxycarbonyl.
BOP: Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.
EtOAc: ethyl acetate
DMF: dimethylformamide
CH_2Cl_2: methylene chloride
$CHCl_3$: chloroform
MeOH: methanol
HOAc: acetic acid

Suitable alternative protecting groups that can be used in the preparation of the present invention include benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, benzyloxycarbonyl, isonicotinyloxycarbonyl, O-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, t-amyloxycarbonyl, isobornyloxycarbonyl, adamantyloxycarbonyl, 2-(4-biphenyl)-2-propyloxycarbonyl and 9-fluorenylmethoxycarbonyl.

In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All variables listed in the Tables below are with reference to the following generic structure:



Example	R^1	R^2	R^3	R^4	R^5	R^6
18		$-CH_2CO_2C_6H_5$	-H	$-(CH_2)_3OCH_3$	$-\overset{O}{\overset{\|}{P}}(OH)_2$	-H
19		-H	$-(CH_2)_2OCH_3$	$-CH_3$	$-\overset{O}{\overset{\|}{P}}(OC_6H_5)_2$	$-C_2H_5$
20		$-CF_2CF_3$	-H	$-C_2H_5$	$-\overset{O}{\overset{\|}{P}}(OC_2H_5)_2$	-H
21		$-(CH_2)_2NH-C_2H_5$	$-CH_3$	$-C_3H_7$	$-\overset{O}{\overset{\|}{P}}(OH)_2$	$-CH_3$
22		$-\overset{O}{\overset{\|}{C}}CH_3$	-H	-t-Bu	$-CO_2H$	-F
23		-H	$-\overset{O}{\overset{\|}{C}}CH_2C_6H_5$	$-CH_2C_6H_5$	$-CO_2CH_3$	-H

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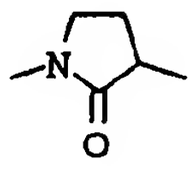
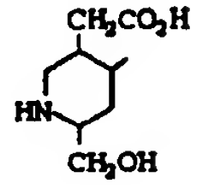
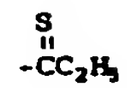
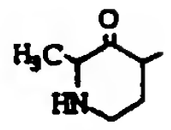
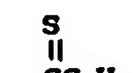
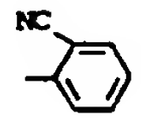
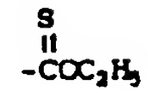
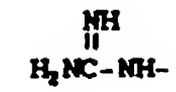
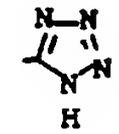
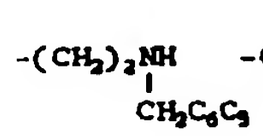
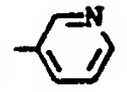
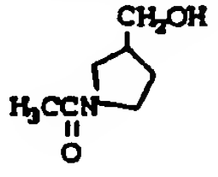
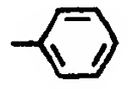
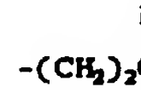
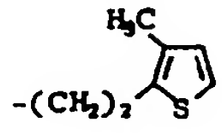
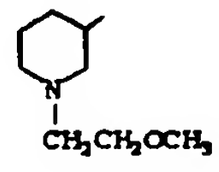
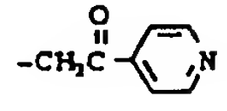
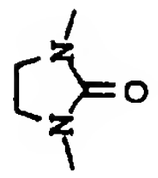
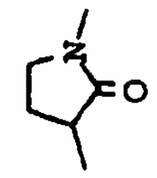
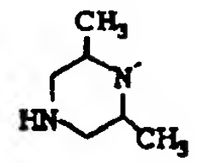
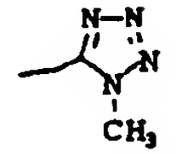
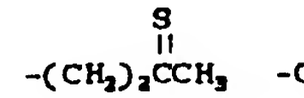
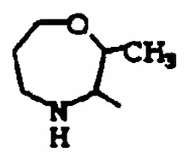
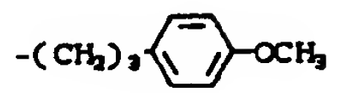
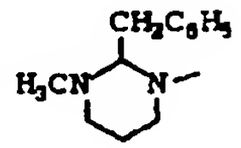
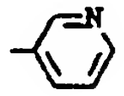
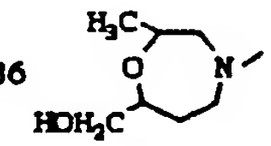
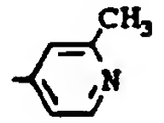
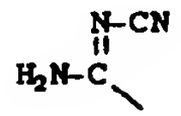
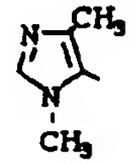
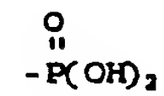
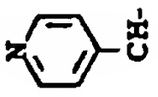
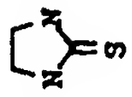
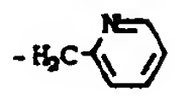
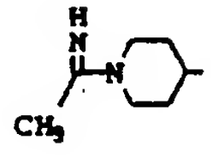
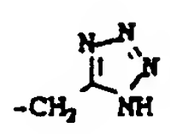
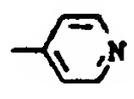
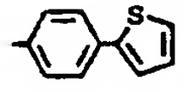
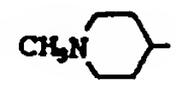
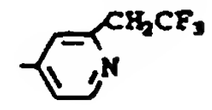
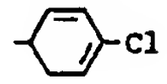
Example	R^7	X	Y	Z	m	n	p
18	$-CH_3$	$-C\equiv C-$	$-\underset{C_6H_5}{\underset{\vert}{CH}}-$	-	1	1	1
19	$-C_6H_5$	$-\underset{CH_2CN}{\underset{\vert}{\overset{CH_3}{\overset{\vert}{C}}}}=C-$	$-\overset{O}{\overset{\Vert}{C}}-NH$	$-CH_2$	2	3	1
20	-H	$-\underset{CH_3O}{\underset{\vert}{CH}}-$	$-NH\overset{O}{\overset{\Vert}{C}}-$	$-\underset{OCH_3}{\underset{\vert}{CH}}-$	4	1	1
21	$-OCH_3$	$-N(C_6H_5)-\overset{O}{\overset{\Vert}{C}}-$	$-CH_2$	$-\underset{OH}{\underset{\vert}{CH}}-$	6	2	2
22	-H	$-\overset{O}{\overset{\Vert}{C}}-NH-C_6H_5$	$-CH_2$	-O-	5	1	5
23	$-CH_3$		$-\underset{CH_3}{\underset{\vert}{CH}}-$	-S-	5	2	2

Example	R^1	R^2	R^3	R^4	R^5	R^6
24			-H	$-(CH_2)_2C_6H_5$	$-CO_2C_4H_9$	$-CF_3$
25		-H				-H
26		$-CH_2SO_2C_6H_5$	$-CF_3$	$-CH_2SO_2CH_3$		$-C_2H_5$
27		-H		$-(CH_2)_2SCH_3$		$-CH_2CO_2C_2H_5$
28			$-CH_3$			-F
29		$-(CH_2)_2CH_2OH$	$-CH_2CF_3$	$-CH_2$ 		-H
30						-Cl
31		$-CH_2CN$	-H		$-CO_2H$	$-CH_2C_6H_5$

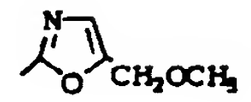
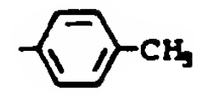
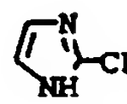
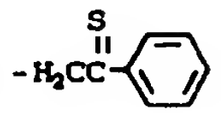
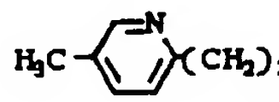
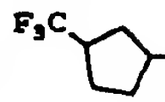
Example	R7	X	Y	Z	m	n	p
24	-H	-O-	C_4H_9 -CH-	-SO-	2	4	3
25	$-OCH_3$	O =C-	$CH_2C_6H_5$ -CH-	$-SO_2-$	1	3	1
26	-CN	S =C-	$CO_2C_2H_5$ -CH-	-NH-	2	2	2
27	-H		-O-	CH_3 -N-	3	3	3
28	$-CH_3$	$-CH_2-$	$CH_2C_6H_5$ -N-	C_6H_5 -N-	4	1	1
29	-H	-S-	CH_3 -CH-	$CH_2C_6H_5$ -N-	0	5	5
30	$-(CH_2)_2C_6H_5$		C_6H_5 -CH-	C_4H_9 -N-	3	2	1
31	-H	CN -CH-	-O-	-	1	2	4

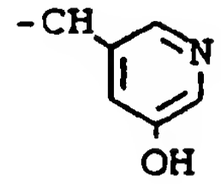
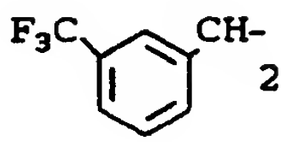
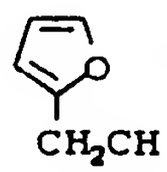
Example	R^1	R^2	R^3	R^4	R^5	R^6
32		-H	$-(CH_2)CN$	$-C_8H_{17}$		$-C_3H_7$
33		$-CH_2OC_6H_5$	$-C_3H_7$		$-CO_2CH_3$	-H
34		-t-Bu	$-CH_2C_6C_5$		$-CO_2H$	$-CH_3$
35			-H	$-CH_3$	$-CO_2H$	$-C_2H_5$
36		-H		$-(CH_2)_3NH_2$	$-CO_2C_4H_9$	$-OC_3H_7$
37		-H	$-C_4H_9$		$-CO_2H$	$-CH_2C_6H_5$
38		$-CH_2C_6H_5$	-H	$-(CH_2)_4OCH_3$	$-CO_2C_2H_5$	$-CH_3$
39		$-(CH_2)_2OCH_3$	$-C_2H_5$			$-CH_2SO_2CH_3$

Example	R'	X	Y	Z	m	n	p
32	-H	$-CH_2-$	$CH_3CO_2CH_3$ -CH-	O = -C-	6	4	6
33				S = -C-	8	2	8
34	-Br	-C- = S		-C=C-	3	1	3
35	-H	$-CH_2-$	$-N(CH_3)-$	O = -C-	1	1	1
36	-H	-C- = S	CH_3CH_2 -N-	-C=C-	2	1	2
37	-H	CH_3 -CH-	-O-	H_3C CH_3 -C=C-	1	2	1
38	$-OCH_3$	CH_3 -C- C_2H_5	$-NCH_3$	C_2H_5 -C=CH-	0	0	5
39	-H	-O-	CH_3 -CH-	-	6	0	6

Example	R^1	R^2	R^3	R^4	R^5	R^6
40	$CH_3CH_2NH-C(=N-CH_3)-NH-$		$-CH_3$	$-CH_2CH_2CO_2$-1-pr	$-P(=O)(OH)_2$	
41		$-CH_2SO_2CH_3$	$-C_6H_5$		$-P(=O)(OCH_3)_2$	-F
42	H_3C-NH-		$-CH_2CO_2CH_3$		$-P(=O)(OC_2H_5)(OH)$	-CN
43	$H_2N-C(=NCH_2C_6H_5)-NH$	$-CH_2SC_6H_5$	$-CH_2OCH_3$	$-(CH_2)_3CH_2OH$	$-P(=O)(OCH_2C_6H_5)_2$	$-C_2H_5$
44	Et_2N-	$-CH_2OC_3H_7$	$-H$	$-(CH_2)_4CO_2H$	$-CO_2H$	$-H$
45		$-(CH_2)_2S(=O)CH_3$	$-OC_2H_5$	$-(CH_2)_3C(=S)-C_2H_5$	$-CO_2$-1-pr	$-CH_2CN$
46		$-(CH_2)_2NHCH_3$	$-CF_3$		$-CO_2C_6H_5$	$-CH_3$
47	$(F_3CH_2C)HN-$	$-H$	$-C_3H_7$	$-C_6H_5$	$-CO_2H$	$-CO_2CH_3$
48	H_2N-	-t-Bu	$-H$		$-CO_2CH_3$	-F

Example	R^7	X	Y	Z	m	n	p
40	$-CH_3$	-NH	$-SO_2$	-O-	2	4	1
41	-OH	$-NCH_2C_6H_5$	$-SO_2$	$-\overset{O}{\overset{\|}{C}}-$	3	1	0
42	-H	$-\overset{S}{\overset{\|}{C}}-$	$-CH_2-$	$-\overset{S}{\overset{\|}{C}}-$	1	1	1
43	-H	$-CH_2-$	$-\overset{S}{\overset{\|}{C}}-$	$-NH\overset{O}{\overset{\|}{C}}-$	3	4	1
44	$-CF_2CF_3$	-O-	$-CH_2-$	$-NH\overset{O}{\overset{\|}{C}}-$	2	0	10
45	-H	$-\overset{H_3C}{\overset{\|}{C}}=\overset{F}{\overset{\|}{C}}-$	$-SO_2$	$-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\|}{N}}-$	1	3	1
46	-OH	$-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\|}{N}}-$	$-CH_2-$	-	10	2	2
47	-H	$-CH_2-$	$-\overset{OH}{\overset{\|}{C}}H$	$-\overset{S}{\overset{\|}{C}}-$	0	2	4
48	$-CF_3$	-NH	$-CH_2-$	$-\overset{O}{\overset{\|}{C}}-$	3	1	2

Example	R^1	R^2	R^3	R^4	R^5	R^6
49	$CH_3NH-C(=NHCH_3)-$	$-CH_2C(=O)CH_3$	-H		$-CO_2C_2H_5$	$-CH_2NO_2$
50	$H_2NC(=NH)-NH$	$-CH_2SC_6H_5$	$-CH_3$	$-C_2H_5$	$-CO_2C_3H_7$	-H
51	$C_2H_5O_2CCH_2CH_2-NH$	$-CF_3$	-H	$-C_4H_7$	$-CO_2CH_2C_6H_5$	
52		$-CH_3$		$-C_5H_{11}$	$-CO_2C(=O)CH_3$	$-OC_4H_9$
53		$-CH_2CN$	-H	$-C_6H_{13}$	$-CO_2COCH_3$	$-CCH_3$ (S)
54	$H_3CC(=S)NH_2CH_2CN-$	$-CH_2CF_3$		$-C_7H_{15}$	$-CO_2COC(CH_3)_3$	-H
55	$H_5C_6CH(H_5C_6H_2C)NH_2CH_2CN-$		$-C_2H_5$	$-C_8H_{17}$	$-CNHCH_2CO_2H$	$-C_6H_5$
56		-H	$-CH_2C_6H_5$	$-C_9H_{10}$	$CNHCH(C_6H_5)CO_2CH_3$	$-CCH_3$ (S)
57	$H_3COOC(CH_2)_2N(CH_2COOH)-$	-H	$-(CH_2)_2C_6H_5$	$-(CH_2)_2-O-C_6H_5$	$-CNHCH(CH_3)CO_2C_2H_5$	$-CF_3$

Example	R^7	X	Y	Z	m	n	p
49	-H	$-CH_2$	$-CH_2$	-	2	2	2
50	$-CH_2NHC(=O)CH_3$	$-CH_2-$	$-N(COCH_3)-$	$-CH(C_4H_9)$	6	0	0
51	-H	-S-	$-CH_2-$	$-CH(CH_3)$	3	1	1
52	$-CH_3$	-SO	$-CH_2-$	-	0	0	5
53	-F	$-SO_2$	-NH	-	8	1	2
54	$-COC_2H_5$ (S)	-C- (O)	-NH	$-CH(C_3H_7)$	4	2	2
55	$-CH_2CCH_3$ (O)	-C- (S)	-NH		6	1	3
56	-F	-CH=CH-	$-NCH_3$		2	2	2
57	-H	$-C\equiv C-$	$-NCH_3$		3	4	1

EXAMPLE 58

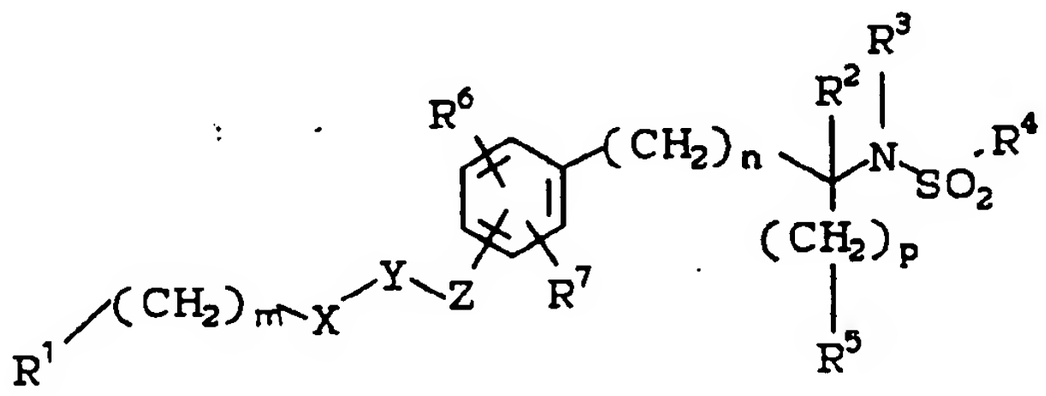
Blood was drawn into 0.1 volumes of acid-citrate-dextrose (85 mM sodium citrate, 64 mM citric acid, 110 mM dextrose) by venipuncture from normal human volunteers. Platelet-rich plasma was prepared by centrifugation at 400 x g for 12 minutes. PGEI (5 mg/ml) was added and platelets were collected by centrifugation at 800 x g for 12 minutes. The platelet pellet was resuspended into human platelet buffer (140 mM NaCl, 7.9 mM KCl, 3.3 mM Na_2HPO_4, 6 mM HEPES, 2% bovine serum albumin, 0.1 % dextrose, pH 7.2) and filtered over Sepharose 2B that was previously equilibrated in human platelet buffer. Platelets were counted and adjusted to 2 x 108/ml with human platelet buffer. Human fibrinogen (10-100 mg/ml and $CaCl_2$ (1 mM) were added and aggregation was initiated by the addition of 10 mM ADP. Aggregation was monitored by the initial rate of increase of light transmittance.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of clotting disorders or emboli, or for other indications for the compounds of the invention indicated above.

Likewise, the specific pharmacological responses observed may vary acording to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

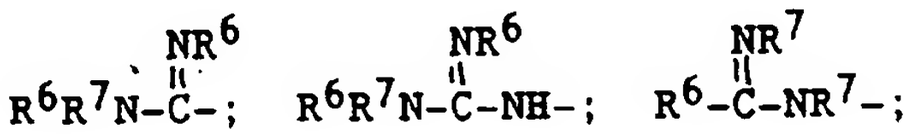
Claims

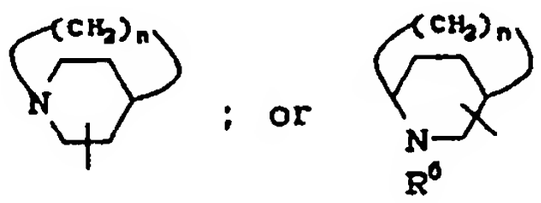
1. A compound of the structural formula



and the pharmaceutically acceptable salts thereof, wherein

R^1 is a four to eight member heterocyclic ring containing 1, 2 ,3 or 4 heteroatoms wherein said heteroatoms are N, O or S and wherein said heterocyclic ring is optionally substituted at any atom by H, R^6 or R^7; NR^6R^7





wherein R^6 and R^7 are independently

hydrogen and

unsubstituted or substituted C_{0-10} alkyl and cycloalkyl wherein said substituents are C_{1-10} alkoxy,

C_{1-10} alkoxyalkyl,
C_{1-10} alkoxyalkyloxy,
C_{1-10} alkoxycarbonyl,
C_{1-10} alkylcarbonyl,
C_{4-10} aralkylcarbonyl,
C_{1-10} alkylthiocarbonyl,
C_{1-10} aralkylthiocarbonyl, thiocarbonyl,
C_{1-10} alkoxythiocarbonyl, aryl,
a 5 to 6 membered saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms wherein said heteroatoms are taken from the group consisting of
N, O and S,
C_{1-4} alkanoylamino,
C_{1-6} alkoxycarbonyl-C_{0-6} alkylamino,
C_{1-10} alkylsulfonylamino,
C_{4-10} aralkylsulfonylamino,
C_{4-10} aralkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthio,
C_{4-10} aralkylthio,
C_{1-10} alkylsulfinyl,
C_{4-10} aralkylsulfinyl,
C_{1-10} alkylsulfonyl,
C_{4-10} aralkylsulfonyl, aminosulfonyl,
C_{1-10} alkylaminosulfonyl,
C_{4-10} aralkylsulfonylamino,
oxo,
thio,
unsubstituted and mono- and di-substituted 1-ethenyl, 2-ethenyl and 3-propenyl wherein said substituents are selected from the group consisting of hydrogen, C_{1-10} alkyl and C_{4-10}
aralkyl,
carboxy,
hydroxy,
amino,
C_{1-6} alkylamino,
C_{1-6} dialkylamino,
halogen, where halogen is defined as F,
Cl, Br or I,
nitro, and
cyano,
and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said substituent is as previously defined for R^6 and R^7;
R^2 and R^3 are independently
hydrogen,
aryl and
unsubstituted and substituted C_{0-10} alkyl and cycloalkyl wherein said substituent is
C_{1-10} alkoxyalkyl,
aryl,
a 4 to 8 membered saturated heterocyclic ring system containing 1, 2, 3 or 4 hetero atoms, wherein said hetero atoms are taken from the group consisting of N, O and S,
C_{4-10} aralkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthio,
C_{4-10} aralkylthio,
C_{1-10} alkylsulfinyl,
C_{4-10} aralkylsulfinyl,

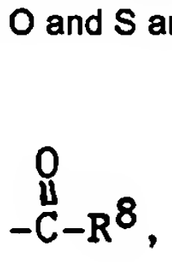
C_{1-10} alkylsulfonyl,
C_{4-10} aralkylsulfonyl, carboxy,
C_{1-10} alkylcarbonyl,
C_{1-10} alkylthiocarbonyl,
C_{4-10} aralkylcarbonyl,
C_{4-10} aralkylthiocarbonyl,
C_{1-6} alkoxycarbonyl,
C_{4-10} aralkoxycarbonyl,
C_{1-6} alkoxy,
C_{1-6} alkoxycarbonyl-C_{1-4} alkyl,
C_{4-10} aralkoxycarbonyl-C_{1-4} alkyl,
C_{4-10} aralkoxy,
C_{1-6} alkylamino,
C_{1-12} dialkylamino,
C_{1-6} alkanoylamino,
C_{4-10} aralkanoylamino,
C_{4-10} aralkylamino,

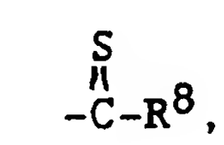
R^4 is

aryl,
C_{1-10} alkyl or cycloalkyl,
C_{4-10} aralkyl,
C_{1-10} alkoxyalkyl,
C_{1-10} alkaryl,
C_{1-10} alkylthioalkyl,
C_{1-10} alkoxythioalkyl,
C_{1-10} alkylamino,
C_{4-10} aralkylamino,
C_{1-10} alkanoylamino,
C_{4-10} aralkanoylamino,
C_{1-10} alkanoyl,
C_{4-10} aralkanoyl, and
unsubstituted or substituted C_{1-10} carboxyalkyl wherein said substituent is aryl or C_{1-10} aralkyl; further wherein any of the substituents for R^4 may be substituted by a substituent selected from the group as defined for R^6;

R^5 is

a four to eight member saturated or unsaturated heterocyclic ring containing 1, 2, 3 or 4 heterocyclic atoms wherein said heteroatoms are N, O and S and

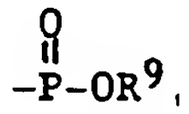


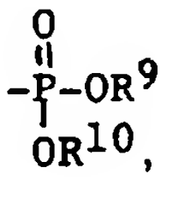


wherein R^8 is

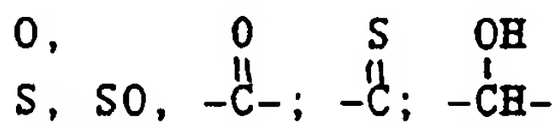
hydroxy,
C_{1-10} alkyloxy,
C_{1-10} alkaryloxy,
C_{4-10} aralkyloxy,
C_{4-10} aralkylcarbonyloxy,
C_{1-10} alkoxyalkyloxy,

C_{1-10} alkoxyalkylcarbonyloxy,
C_{1-10} alkoxycarbonylalkyl,
C_{1-10} alkylcarbonyloxyalkyloxy,
an L- or D-amino acid joined by an amide linkage or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is esterified by C_{1-6} alkyl or C_{4-10} aralkyl,

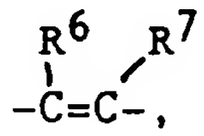




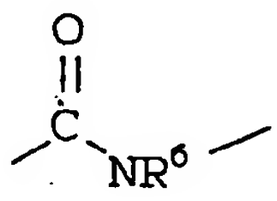
wherein R^9 and R^{10} are selected from the group consisting of hydrogen, C_{1-10} alkyl and C_{4-10} aralkyl;
X and Y are optional substituents that, when present are independently
NR^6,



SO_2,

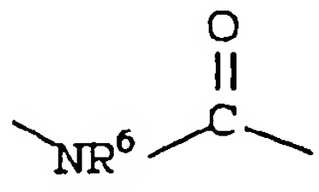


-C≡C-,
a 4- to 8-membered ring containing 0, 1, 2, 3 or 4 heteroatoms chosen from N, O and S, wherein said ring is independently substituted at any atom with R^6
aryl,
or



;

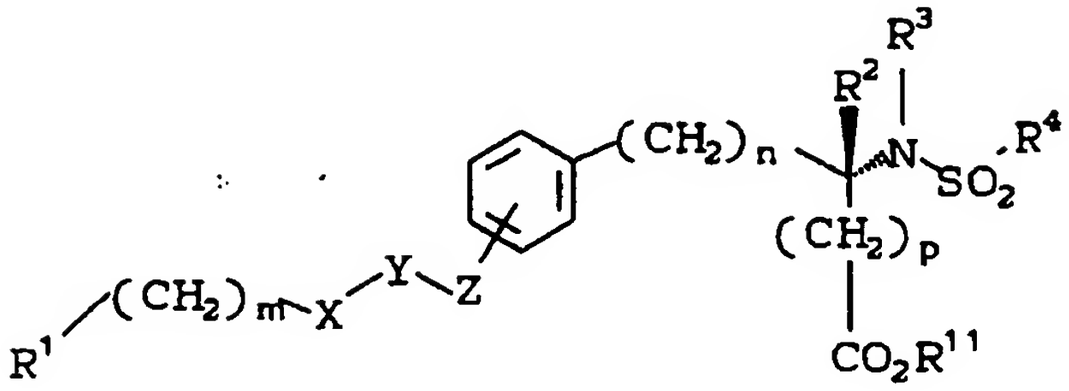
$-NR^6SO_2-$; $-SO_2NR^6-$; or



;

Z is an optional substituent that, when present, is independently chosen as defined for X and Y;
m is an integer of from zero to ten;
n is an integer of from zero to ten; and
p is an integer of from zero to three.

2. A compound of the structural formula



and the pharmaceutically acceptable salts thereof, wherein
R^1 is
a four to eight member heterocyclic ring wherein said heteroatoms are N, O or S and wherein said heterocyclic ring is optionally substituted by C_{1-10} alkyl; or
NR^6R^7 wherein R^6 and R^7 are independently
hydrogen,
unsubstituted or substituted C_{1-10} alkyl wherein said substituent is
C_{1-10} alkoxycarbonyl,
aryl,
C_{0-5} dialkylamino-C_{1-10} alkyl,
C_{4-10} aralkyl,
and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said substituent is as previously defined for R^6 and R^7;
R^2 and R^3 are independently
hydrogen,
C_{1-4} alkyl or C_{4-10} aralkyl;
R^4 is
aryl,
C_{1-10} alkyl or cycloalkyl,
C_{4-10} aralkyl,
C_{1-10} alkoxyalkyl or
unsubstituted or substituted C_{1-10} carboxyalkyl wherein said substituent is aryl or C_{1-10} aralkyl;
R^{11} is
hydrogen or
C_{1-10} alkyl;
X and Y are independently
0,
SO_2,

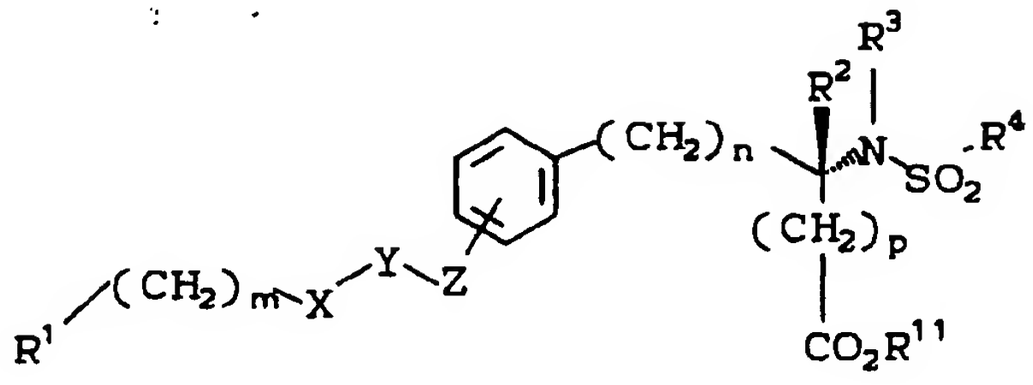
$$-CH=CH-,\ -\overset{O}{\overset{\|}{C}}NR^6-,\ -NR^6\overset{O}{\overset{\|}{C}}-,\ SO_2NR^6-,\ \text{or}\ -NR^6SO_2-$$

aryl,
a 5- or 6-membered ring containing 0, 1 or 2 heteroatoms chosen from N, O and S wherein said ring is independently substituted at any atom with R^6;
Z is an optional substituent that, when present, is

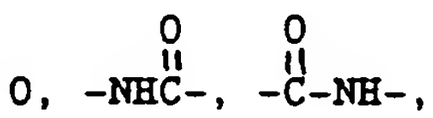
$$O,\ SO_2,\ -NR^6CO-,\ -CONR^6-,\ -\overset{O}{\overset{\|}{C}}-$$

C_{1-10} straight or branched alkyl;
m is an integer of from zero to eight;
n is an integer of from zero to two; and
p is an integer of from zero to two structural formula

3. A compound of the structural formula

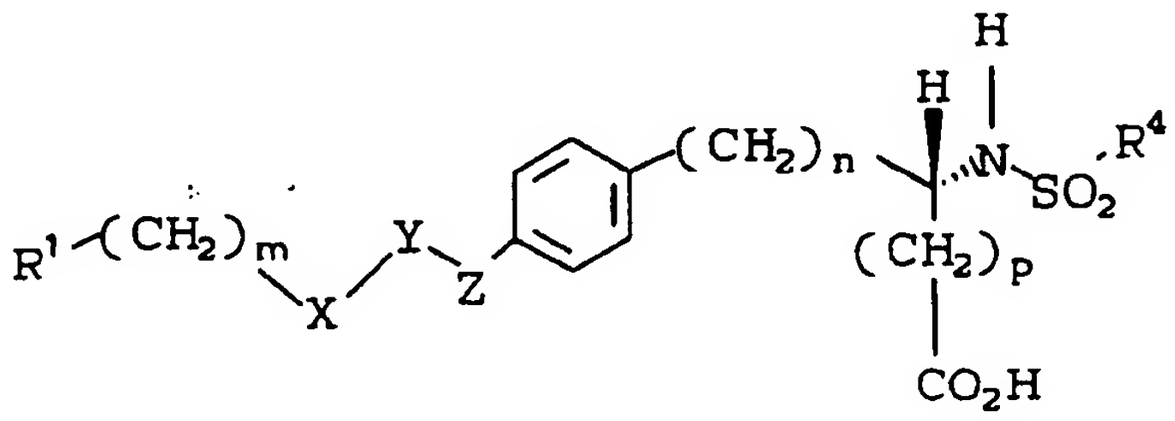


and the pharmaceutically acceptable salts thereof, wherein
R^1 is
a five to six member heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N,O or S and wherein said heterocyclic ring is optionally substituted by C_{1-5} alkyl; or
NR^6R^7 wherein R^6 and R^7 are independently
hydrogen,
unsubstituted or substituted C_{1-10} alkyl wherein said substituent is C_{4-10} aralkyl,
and further wherein said N can additionally be substituted to form a quaternary ammonium ion wherein said substituent is as previously defined for R^6 and R^7;
R^2 and R^3 are hydrogen;
R^4 is
aryl,
C_{1-10} alkyl,
C_{4-10} aralkyl,
R^{11} is
hydrogen or
C_{1-10} alkyl;
X and Y are independently



-CH=CH-, $-CH_2-$, or C_{1-10} cycloalkyl;
Z is an optional substituent that, when present, is
O, SO_2, -NHCO-,
C_{1-10} straight or branched alkyl;
m is an integer of from zero to six;
n is an integer of from zero to one; and
p is an integer of from zero to one.

4. A compound of the structural formula



and the pharmaceutically acceptable salts thereof, wherein

R^1 is

a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N or O and wherein said heterocyclic ring is optionally substituted by C_{1-3} alkyl; or

NR^6R^7 wherein R^6 and R^7 are independently

hydrogen or

C_{1-10} alkyl;

R^4 is

aryl,

C_{1-10} alkyl or

C_{4-10} aralkyl;

X and Y are independently

C_{1-10} alkyl or cycloalkyl

Z is an optional substituent that, when present, is

O, -NHCO-, or -CONH-

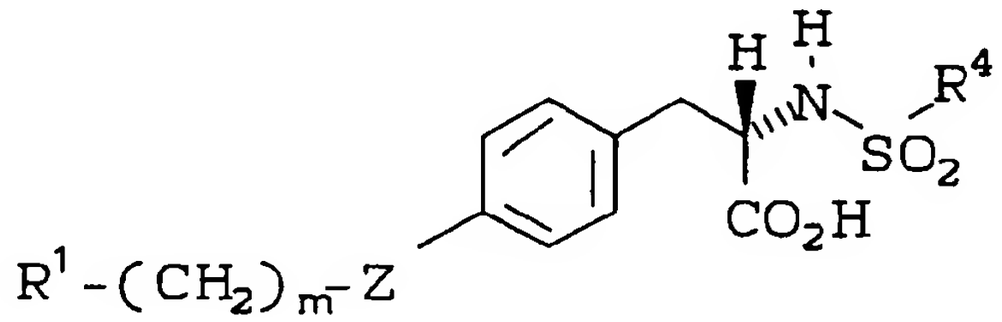
C_{1-5} straight or branched alkyl;

m is an integer of from zero to six;

n is one or two; and

p is zero or one.

5. A compound of the structural formula



wherein

R^1 is

a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N;

NR^6R^7 wherein R^6 and R^7 are independently

H or

C_{1-10} alkyl;

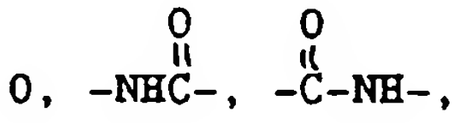
R^4 is

aryl

C_{1-10} alkyl

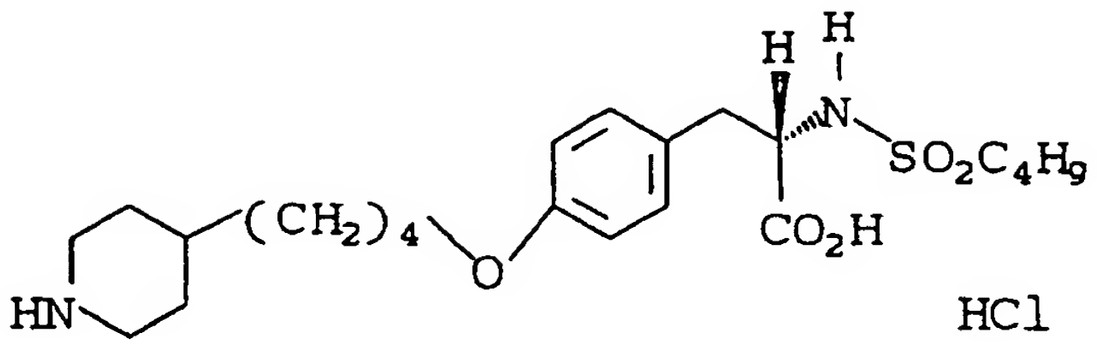
C_{4-10} aralkyl;

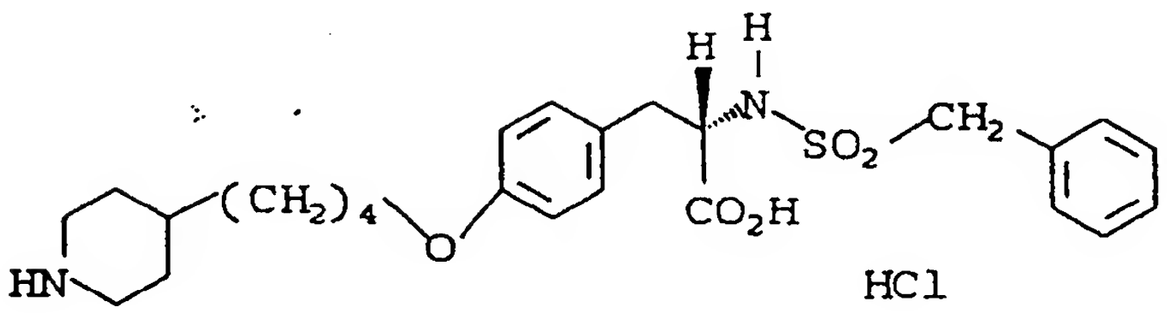
Z is

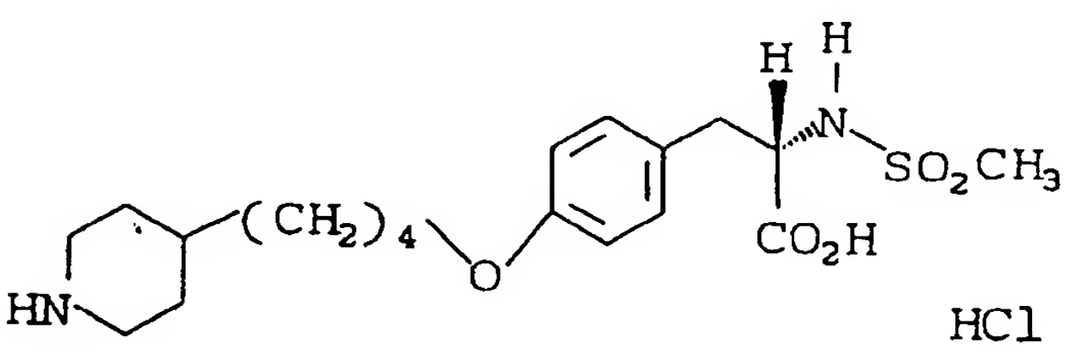


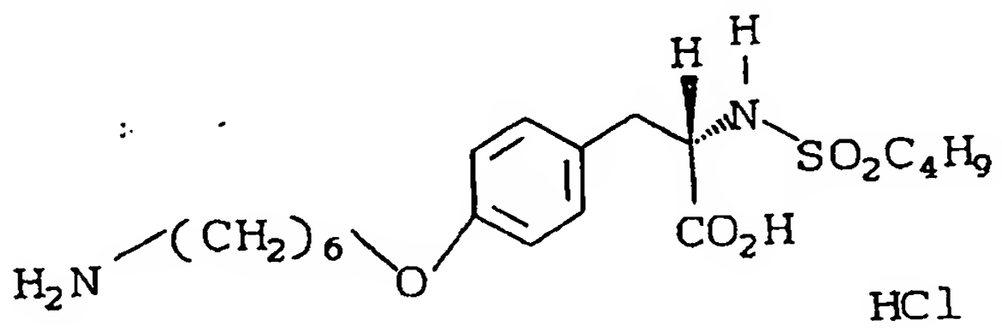
where m is an integer from two to six.

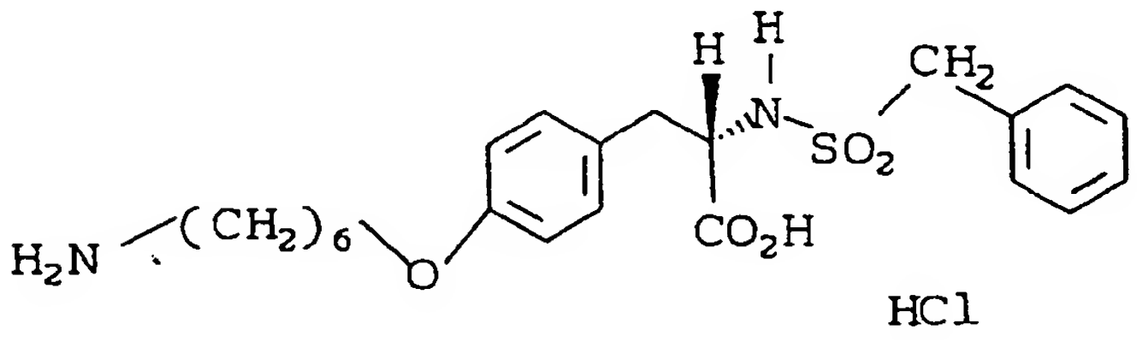
6. A compound as claimed in Claim 5, of the structural formula











7. A pharmaceutical composition comprising a compound as claimed in Claim 1 or Claim 6 and a pharmaceutically acceptable carrier.

8. The use of a compound as claimed in Claim 1 or Claim 6 for the manufacture of a medicament for blocking fibrinogen from acting as its platelet receptor site in a mammal.

9. The use of a compound as claimed in Claim 1 or Claim 6 for the manufacture of a medicament for the prevention or treatment of thrombus formation.

10. The use of a compound as claimed in Claim 1 or Claim 6 together with an anti-coagulant agent for blocking fibrinogen from acting at its platelet receptor site in a mammal.

11. The use of a compound as claimed in Claim 1 or Claim 6 together with an anti-coagulant agent for the prevention or treatment of thrombus formation.

12. The use of a compound as claimed in Claim 1 or Claim 6 together with a fibrinolytic agent for blocking fibrinogen from acting at its platelet receptor site in a mammal.

13. The use of a compound as claimed in Claim 1 or Claim 6 together with a fibrinolytic agent for the prevention or treatment of thrombus formation.

14. The use of a compound as claimed in Claim 1 or Claim 6 together with a platelet anti-aggregation agent for blocking fibrinogen from acting at its platelet receptor site in a mammal.

15. The use of a compound as claimed in Claim 1 or Claim 6 together with a platelet anti-aggregation agent for the prevention or treatment of thrombus formation.

16. The composition as claimed in Claim 7, further comprising at least one compound selected from the group consisting of platelet anti-aggregation agents, thrombolytic agents and anti-coagulation agents.